Endocrinology, Nutrition, and Growth Branch

NICHD

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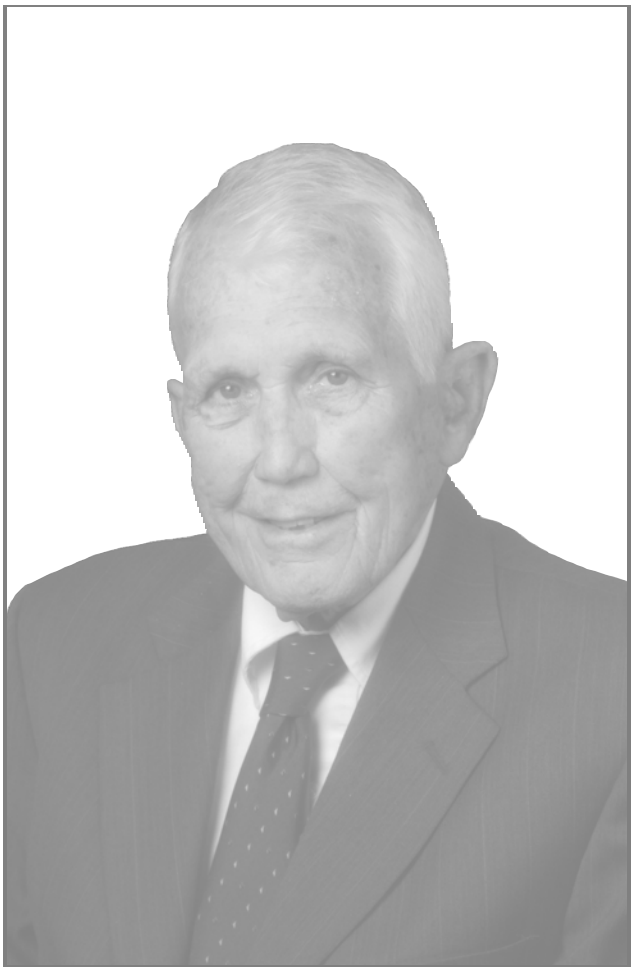

Modifications of the molecular environment markedly alter human development. …Environmental improvement will be made, and the immature will be aided in their development just as surely as the four-minute mile was conquered.

——Dr. Robert E. Cooke

Anticipatory Pediatrics, 1966

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EXECUTIVE SUMMARY

The Endocrinology, Nutrition, and Growth Branch (ENGB) is pleased to present a summary of its activities to the National Advisory Child Health and Human Development (NACHHD) Council. The ENGB is one of four branches within the Center for Research for Mothers and Children (CRMC). The Branch provides the National Institute of Child Health and Human Development (NICHD) with a focus for research and research training in nutritional science, childhood antecedents of disease, developmental endocrinology, developmental neuroendocrinology, and physical growth and body composition. Research in these areas of scientific endeavor is directed toward laying the groundwork for future health.

Historically, another major research emphasis for the ENGB has involved pediatric pharmacology and the development of better and safer drug therapies for pregnant women, newborns, children, and adolescents. To ensure that this work is as focused as possible, the NICHD created the Obstetric and Pediatric Pharmacology Branch (OPPB) in April 2004. All ENGB-supported research in this area was transferred to the new Branch at that time; this report includes information on activities supported by the ENGB up to that date.

PREVENTION OF CHRONIC DISEASE

The burdens of obesity, cardiovascular disease, diabetes, and osteoporosis continue to increase in this country and abroad. These chronic diseases have their roots in childhood. Because these conditions are difficult or impossible to reverse in adulthood, the ENGB encourages research on preventing their onset during childhood.

Obesity: The Branch has provided long-term support to scientists who are working to elucidate the genetic, environmental, and behavioral origins of obesity. The Branch recently expanded these efforts by publishing a request for applications (RFA) on prevention and treatment of childhood obesity in primary care settings, as well as a program announcement (PA) on school-based initiatives to prevent childhood obesity. The National Institutes of Health (NIH) director highlighted the agency's commitment to the obesity epidemic by forming the NIH Obesity Research Task Force in 2003; staff of the ENGB have played a prominent role in this trans-NIH effort. The ENGB also established an NICHD working group on obesity that includes members from all the Institute's Centers, Divisions, and Programs; this working group recently developed a research initiative to address the origins and consequences of maternal obesity during pregnancy.

Atherosclerosis: Over the past decade, the Branch has supported research on identifying children who are susceptible to premature coronary artery disease. These efforts have revealed predictive markers that are being incorporated into the revised National Cholesterol Education Program guidelines for children and adolescents, scheduled for release in 2006. This research showed that the risk of early atherosclerosis increases markedly according to the number of predictive markers. The Branch expanded this research initiative by holding three research-

planning workshops on risk factors in childhood, and by issuing an RFA on the precursors of the metabolic syndrome in childhood.

Diabetes: In an effort to prevent diabetes, the Branch has pioneered immunogenetic methods that stratify levels of risk for type 1 diabetes mellitus (T1DM), also called juvenile diabetes. This work forms the basis of the Diabetes Prevention Trial, TrialNet, and the Trial to Reduce T1DM in the Genetically at Risk (TRIGR). These trials aim to prevent or delay the onset of T1DM in relatives of index cases. The ENGB also supports the Prospective Assessment of Newborns for Diabetes Autoimmunity (PANDA). Investigators in charge of PANDA recently identified the first gene directly involved in the autoimmune attack on the beta cells of the pancreas in diabetes. The ENGB also established the Diabetes Research in Children Network (DirecNet), the world's first research network to focus on diabetic children, in order to monitor levels of plasma glucose non-invasively, and to prevent attacks of hypoglycemia.

The ENGB also supports research aimed at preventing type 2 diabetes mellitus (T2DM). Research projects initiated in response to an RFA on T2DM in the pediatric population elucidated susceptibility genes and other risk factors involved in the epidemic of T2DM in adolescents. Investigators reported a 25-percent prevalence of glucose intolerance among obese children (Sinha et al 2002) and correlated visceral adiposity in children with new markers of beta-cell failure and impending T2DM (Bacha et al 2004).

The NICHD continues its support of the Hyperglycemia and Pregnancy Outcome (HAPO) study, an international study in 11 countries of more than 25,000 pregnant women and their offspring. This effort studies the glycemic state of these women in relation to the need for cesarean section, and in regard to the occurrence of hypoglycemia in the newborn offspring.

Osteoporosis: In response to an RFA on behavioral strategies to prevent osteoporosis later in life, investigators are studying the bone mineral density (BMD) of several thousand children, prospectively, to assess the effect of dietary and behavioral interventions. The ENGB also initiated the BMD in Childhood Study (BMDCS), a population-based longitudinal study of bone accretion in 1,550 children, from ages six to 16, to further understand this topic.

ENDOCRINOLOGY

Pediatric Endocrinology: Pediatricians now have access to the results of a 16-year randomized, double-blind, placebo-controlled study designed to ascertain the effect of human growth hormone (hGH) on final height in short children who are not hGH deficient (Leschek et al 2004). The study received much attention in the lay press and was used by a Food and Drug Administration (FDA) advisory committee to recommend that hGH be labeled for this new indication. The trial was designed at an ENGB-supported conference on disorders of human growth and stands as an example of cooperation between extramural and intramural scientists at the NICHD.

Molecular Biology of hGH and Its Receptor: Research on the evolutionary origins of hGH and its receptor protein have led to a remarkable set of discoveries about transposable elements in the human genome, and about how genes evolve to code for more than one protein (Li et al 2001).

Growth Factors: The Branch funds research on the functions of epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and their receptors. (For a discussion of the history of research support on EGF, see Appendix D.) This research has led to an understanding of post-receptor intracellular events and to clinical applications of growth factors. For instance, EGF is now used to treat corneal ulcers and severe burns, and EGF-receptor activity is used to plan regimens of chemotherapy for treating breast cancer. In animal models, bFGF crosses the blood-brain barrier and stimulates neurogenesis; it also stimulates stromal cells of human bone marrow to differentiate into neurons, thus providing a reservoir of cells that may be used to treat degenerative neurologic diseases of the brain and spinal cord.

Intersex Conditions: The Branch recently sponsored a research-planning workshop on intersex conditions in infants and children that led to the formation of a network of interested clinical investigators (Meyer-Bahlburg & Blizzard 2004).

NUTRITION

Infant Nutrition: The Branch supports research on the pressing issues of nutrient requirements and optimal feeding regimens for infants of very low and extremely low birth weights. The Branch also supports research on understanding the effects of essential fatty acids on visual acuity and brain development and on the antimicrobial effects of breast milk, with the aim of developing a new class of antibiotics.

Maternal-Fetal Nutrition: Observations on the fetal origins of hypertension and atherosclerosis have energized the field of maternal-fetal nutrition. Following an NICHD-funded international research conference on the fetal origins of adult disease, the ENGB issued an RFA on maternal-fetal nutrition and is now funding six innovative studies in this fertile area of research.

The placental origin of intrauterine growth retardation (IUGR) is an important, but understudied area of research. The Branch encourages research on the role of placental nutrient transporters in the net transfer of nutrients to the fetus. Mutations in the genes that code for nutrient transporters are also of interest to the ENGB and will be the focus of future initiatives.

Necrotizing Enterocolitis (NEC): Because NEC remains a lethal disorder for preterm infants, the ENGB targets this intestinal disorder of newborns as a high research priority. The Branch is funding research on optimal therapeutic strategies to employ in severe cases of NEC. The Branch also supports studies of NEC in animal models, including studies that use EGF to treat the disorder.

GROWTH AND DEVELOPMENT

The Fels Longitudinal Study of Growth and Development has followed more than 1,400 individuals, who were enrolled at birth, beginning in 1930. The Fels Study provided growth data for the North American Standard Tables of Height and Weight, as well as for a comprehensive atlas of bone age and skeletal development. These standards are in widespread use in the United States and abroad. The Fels database is now being used to ascertain the origins of the metabolic syndrome in childhood, by examining childhood data of adults currently diagnosed with the metabolic syndrome (Sun et al 2004).

The Child Health and Development Study (CHDS) of 20,000 pregnancies began in 1959, as a companion to the Perinatal Collaborative Study. The NICHD provides support to maintain the CHDS database and serum collection. Investigators who are interested in maternal and placental origins of disease later in life currently use these resources, especially in the study of long-term effects of *in utero* exposure to organochlorines, such as dichlorodiphenyltrichloroethane or DDT (Cohn et al 2003).

PEDIATRIC PHARMACOLOGY

Fewer than one-quarter of the medications currently on the market have been approved by the FDA for use in children. To rectify this imbalance, the ENGB initiated the Pediatric Pharmacology Research Unit (PPRU) Network as a national resource to facilitate clinical studies of drugs in infants and children. As of June 2004, the PPRU Network had initiated more than 216 studies of drugs in pediatric populations, working closely with more than 54 different pharmaceutical firms in the United States and abroad. The success of the Network spurred congressional legislation mandating pediatric drug studies for all new drug applications submitted to the FDA for approval. In April 2004, the NICHD established the OPPB within the CRMC and transferred the PPRU Network to the new Branch.

CHILD HEALTH RESEARCH CAREER DEVELOPMENT AWARDS (CHRCDA)

The creation of a congressionally mandated program of Child Health Research Centers (CHRCs) in 1990 was a major development in pediatric science in the United States. CHRCDAs aim to accelerate the application of discoveries in basic research to the care of sick children. Currently, 20 centers receive support through this mechanism. The CHRCs are also instrumental in training the next generation of academic pediatricians and have launched the careers of 485 pediatric scientists in 14 subspecialties (Winer et al 2001).

OVERVIEW OF BRANCH FUNDING

In the fiscal year ending September 30, 2003, the Branch supported 257 research projects at a level of $68.2 million. Figure 1 analyzes these projects by subject matter. Approximately one-half of the Branch budget addresses research and training in nutrition and in the antecedents of adult disease, while one-quarter supports research and training in developmental endocrinology. The remaining one-quarter supports research on physiology and physical growth, as well the 20 CHRCs and the 13 PPRUs. Since its report to the Council in September 2000, the ENGB research budget has grown by $21 million. Support for the research program on fetal origins of adult disease accounts for $3 million of the increase, while an additional $2 million represents support for new research projects on obesity and the metabolic syndrome. The BMDCS and DirecNet account for an additional $8 million and support for HAPO, TRIGR, and PANDA collectively account for $5 million of the increase. Support for new initiatives in pediatric pharmacology accounts for the remainder of the increase.

PREVENTION OF CHRONIC DISEASE

Obesity, diabetes, atherosclerosis, and osteoporosis are the products of gene-environmental interactions that determine disease susceptibility. Advances in genomics, proteomics, and informatics make possible a concerted attack on the origins of these diseases, leading to the development of markers that predict disease susceptibility. Microarray chip technology now permits analyses of the simultaneous expression of tens of thousands of genes. By documenting differential gene expression, researchers can elucidate the earliest divergent biochemical pathways that lead to disease later in life. Understanding these pathways will provide new targets for intervention.

ATHEROSCLEROSIS

Coronary atherosclerosis remains the primary cause of death in the United States today, often causing death during the most productive years of life. An estimated 1.2 million people in the United States have heart attacks each year, about one every 25 seconds (American Heart Association 2004).

Dr. Robert Cooke, who was instrumental in the founding of the NICHD, practiced anticipatory pediatrics, a concept that rests on tailoring the nutritional-biochemical environment to each child's genotype (Cooke 1966). Dr. Cooke's anticipatory approach to disease led him to assert that atherosclerosis was a pediatric disease. In order to develop this concept, the ENGB provided funding for the Bogalusa Heart Study, the Rochester Family Heart Study, and the San Antonio Family Heart Study to develop markers that predict the early onset of atherosclerosis in high-risk children.

These studies showed that the extent of early atherosclerotic lesions correlated with body mass index (BMI), systolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, and serum triglyceride concentrations. The amount of arterial surface covered by plaques varied with the number of risk factors, increasing by 12-fold in those with four risk factors compared to those with none (Berenson et al 1998). The studies also showed that early-onset ischemic heart disease was associated with higher plasma fibrinogen (Greenlund et al 1999) and higher homocysteine levels (Shea et al 1999).

To build on these findings, the ENGB sponsored three research-planning workshops to ascertain precursors of cardiovascular disease in children and adolescents. Participants emphasized the need to study clusters of risk factors, and to mine data from established cohort studies. (For a list of these and other workshops organized and sponsored by the ENGB, see Appendix A.)

In addition, new data from the Fels Longitudinal Study documented the onset of low plasma high-density lipoprotein (HDL) cholesterol levels and high plasma triglyceride levels in boys, but not in girls, as early as age 12. Childhood data from Fels participants who, as adults, have the metabolic syndrome show deleterious levels of HDL-cholesterol and plasma triglycerides as early as age 13 in both boys and girls (Sun et al 2004). Other research has shown that low levels of adiponectin, which serves as an anti-inflammatory agent and as an insulin sensitizer, can be used to predict the early onset of atherogenesis (Bacha et al 2004).

In 2003, the ENGB published an RFA entitled *Establishing the Precursors of the Metabolic Syndrome in Childhood*. Three studies were funded as a result of this RFA: one is examining the offspring of Mexican Americans enrolled in the San Antonio Family Heart Study; one is focusing on the interaction between birth weight and race in generating cardiovascular risk factors; and one is evaluating the interaction of cardiovascular disease susceptibility genes and the environment in 1,000 pairs of monozygotic and 1,000 pairs of dizygotic twins in their second and third decades of life. These major studies are expected to develop markers for early atherogenesis and to identify new targets for early intervention.

DIABETES

Type 1 Diabetes Mellitus (T1DM)

T1DM affects one in 300 people in the United States and accounts for much of the costly retinal, renal, neurologic, and cardiac diseases treated in this country every year. Research supported by the Branch established T1DM as an autoimmune disorder with a strong genetic component. Branch-supported immunogenetic research showed that, in genetically susceptible individuals, glutamic acid decarboxylase and tyrosine phosphatase, key enzymes involved in beta-cell activity, were targeted by an autoimmune attack. Investigators all over the world are now using these immunological markers to establish the risk of T1DM in relatives of index cases. Successful identification of the prediabetic state presents the prospect of treating high-risk children with vaccines and other immunomodulators before the onset of clinical disease.

Prospective Assessment in Newborns for Diabetes Autoimmunity (PANDA)

The ENGB partnered with the Juvenile Diabetes Research Foundation in a study of 23,000 infants who are at genetic risk for diabetes to detect the earliest changes in gene expression in the pathogenesis of T1DM. This study has disclosed an important immunogenetic basis for the autoimmune attack on the pancreatic insulin-producing beta cells (Guo et al 2004). PANDA investigators identified a single nucleotide mutation in a gene that codes for a small ubiquitin-like modifier protein (SUMO-4). SUMO-4 binds to a transcription factor involved in controlling the expression of an interleukin (IL), IL-12B; faulty binding by the mutated protein doubles the expression of the IL-12B gene, thereby initiating or augmenting an autoimmune attack on the beta cells. These findings implicate a new cytokine pathway in the pathogenesis of T1DM that may be a target for novel therapy.

The ENGB recently worked with staff from the National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK) to issue an RFA encouraging investigators to exploit developments in proteomics and bioinformatics. In response, PANDA investigators are now initiating studies of the evanescent proteins that are present during the earliest autoimmune attack on beta cells. This high-technology research should reveal new targets and pathways for the development of rational molecular interventions.

Trial to Reduce T1DM in the Genetically at Risk (TRIGR)

TRIGR is a randomized, controlled clinical trial designed to ascertain if the onset of T1DM can be delayed or prevented by weaning genetically susceptible infants to Nutramigen®, a hydrolysate of cow milk protein, instead of to a standard cow milk-based infant formula. The rationale for this intervention comes from studies in which hydrolyzed protein diets prevented the onset of T1DM in animal models. TRIGR is enrolling 2,032 genetically susceptible infants at 73 sites in 15 countries. The primary outcome will be the prevalence of T1DM in each of the two groups in 2011. Interim analyses, planned for 2005 and 2008, will examine autoantibodies directed against islet-cell antigens in the two groups.

Although the NICHD is the lead Institute for TRIGR, funding for this large trial comes from eight other sources, which greatly leverage the NICHD's contribution. For instance, the Mead Johnson Company is contributing all of the formula for the trial and has prepared package inserts in 12 languages. This trial is the first large effort designed to ascertain if a simple nutritional intervention during infancy can delay or prevent the onset of T1DM in children at high genetic risk for the disease. If the intervention succeeds, the public health implications will be great.

New Directions in T1DM Research

Language in the Senate Appropriations Report for fiscal year 2003 encouraged the NICHD to expand its research on newborn screening tests, specifically to determine the causes of T1DM, and to develop methods to prevent the disease. The report also noted efforts to develop a vaccine to prevent T1DM and urged the NICHD to collaborate with the NIDDK in this important research initiative.

In response to this congressional directive, the NICHD increased the enrollment in PANDA from 12,000 to 23,000 infants. PANDA investigators are screening newborns for the appearance of beta-cell autoimmunity, and for the appearance of unique expression profiles for 200 genes that

promote the autoimmune attack on pancreatic beta cells. This important trial will serve as a model for high-throughput screening programs.

The NICHD also joined the National Institute of Allergy and Infectious Diseases and the NIDDK in an effort to prevent T1DM in children who are at risk for the disease, or to slow the course of beta-cell destruction in children with the disease. The NICHD has committed $2 million per year to support these efforts in TrialNet, a network of 18 clinical centers in the United States, Canada, Europe, and Australia, and in the Cooperative Study Group for Autoimmune Disease Prevention. Initiatives are now under way to test the efficacy of mycophenolate mofetil and daclizumab in mitigating the beta-cell autoimmune attack in cases of newly diagnosed T1DM. Myophenolate mofetil inhibits lymphocyte proliferation by blocking guanosine nucleotide synthesis and, thus, interfering with DNA assembly and T-cell replication. Daclizumab is a monoclonal antibody that binds to the IL-2 receptor on T cells, making them inactive and thereby attenuating the autoimmune siege on the beta cells of the diabetic pancreas.

ENGB staff also represent the NICHD on the congressionally established Diabetes Research Working Group, which implements the Special Statutory Funding Program for T1DM research. Congress initiated this highly focused funding program in fiscal year 1998, and funding will continue through fiscal year 2008.

The Diabetes Research Working Group emphasized the need to increase basic research on the control and regulation of islet-cell differentiation, and to devise methods to stimulate growth and regeneration of islet cells (Diabetes Working Group 1999). In response to this directive, the ENGB has supported pioneering research on the roles played by transcription factors, such as PDX-1, neurogenin 3, and BETA2/neuroD, in determining islet-cell lineage from undifferentiated endodermal cells to insulin-producing beta cells (Kritzik et al 2000; Huang et al 2000). This research holds out the promise of stimulating pancreatic ductal cells to differentiate into functioning beta cells in both T1DM and T2DM. Research supported by other agencies has shown that endogenous precursor cells exist in the pancreas and give rise to new beta cells after elimination of the autoimmune attack by donor spleen cells (Kodama et al 2003). These basic studies were the focus of an exciting meeting on islet-cell transplant that was held in December 2004, and was co-sponsored by the NICHD. Participants emphasized the possibility of actually curing T1DM. Investigators in this promising area embrace the motto of the Juvenile Diabetes Research Foundation: “Insulin is not a cure.”

Diabetes Research in Children Network (DirecNet)

In 2001, staff of the ENGB successfully competed for special statutory funds to create DirecNet, which consists of five diabetes centers working together to develop and test non-invasive ways to monitor children with T1DM for episodes of hypoglycemia that attend intensive insulin therapy. The incidence of hypoglycemia in adolescents who receive intensive insulin therapy is three times that of adults. The risk of hypoglycemia is the main obstacle to successful management of diabetic children of all ages.

Specific goals for DirecNet include assessing the accuracy, efficacy, and effectiveness of continuous monitoring devices used by children with T1DM. In addition, the Network has evaluated the frequency of hypoglycemia to determine the extent to which children’s exercise

contributes to the risk of the condition. DirecNet also focuses on possible changes in neurocognitive function that may be engendered in children with T1DM by frequent bouts of hypoglycemia. In its first three years of operation, DirecNet generated 17 published abstracts and seven published articles about the strengths and weaknesses of using non-invasive monitors in children with T1DM for assessing episodes of hypoglycemia and hyperglycemia. (See Appendix B for the DirecNet bibliography.) Because little is known about daily fluctuations in plasma glucose levels in non-diabetic children, DirecNet investigators also studied this issue and found that most children maintained their levels of plasma glucose within a surprisingly narrow range (98 +/-13 mg/dL) and rarely experienced plasma glucose levels below 70 mg/dL (DirecNet Study Group 2004).

Inhaled Insulin Therapy

The PPRU Network recently conducted an innovative study entitled *Tolerability and Pharmacokinetics of Inhaled Insulin in Children Six to 11 Years of Age with T1DM.* The trial showed that inhaled insulin was as efficacious as regular insulin, injected subcutaneously, thereby establishing a milestone the treatment of diabetes. Availability of this mode of administration will improve children's compliance with intensive insulin therapy and will ameliorate their level of glycemic control. Inhaled insulin should soon replace the subcutaneous injections of regular insulin that many diabetic children need to take before meals.

Type 2 Diabetes Mellitus (T2DM) and the Diabetes Prevention Program

The ENGB, in conjunction with the National Center on Minority Health and Health Disparities and the NIDDK implemented a randomized clinical trial evaluating the efficacy of interventions designed to prevent the onset of T2DM in 4,000 individuals who were at risk for the disorder. National health surveys (Harris et al 1998) show that the percentage of African Americans with diabetes has increased markedly since 1972, so African Americans in the study population were enrolled at twice their national representation. Women with gestational diabetes mellitus (GDM) were also oversampled because of their propensity to develop T2DM within a decade of the index pregnancy.

The results of the trial showed that subjects taking metformin reduced their rate of conversion to T2DM by 31 percent, and that subjects exposed to a lifestyle intervention of diet and exercise slowed their rate of conversion to T2DM by 58 percent (Knowler et al 2002). These welcome findings were announced at a press conference held by the secretary of the U.S. Department of Health and Human Services (DHHS). The guiding concepts of the study are being implemented in obesity clinics throughout the country.

The NICHD co-sponsored an RFA entitled *Type 2 Diabetes in the Pediatric Population* to ascertain the causes for the alarming increase in the incidence of T2DM among children and adolescents. Between 1982 and 1994, the incidence of T2DM in this population grew by a factor of 10 (Pinhas-Hamiel et al 1996). Studies funded in response to the RFA revealed that up to 25 percent of obese children are glucose intolerant, a finding that has vast implications for the nation's future health.

The finding of glucose intolerance in obese children presages the onset of frank diabetes in their second or third decade of life, with attendant eye, kidney, heart, and nerve damage (Sinha et al

2002). In an editorial, Rocchini (2002) emphasized, "There is an emerging pediatric epidemic of type 2 diabetes. If this epidemic cannot be averted, its full public health effect will be felt as affected children become adults and the long-term complications of diabetes develop." The approach embodied in this study is being implemented in pediatric obesity clinics across the nation.

Racial Disparities in T2DM

In an effort to understand the factors that contribute to the racial disparity in susceptibility to T2DM, Gower et al (2003) analyzed the contributions of 20 ancestral African alleles versus 20 ancestral European alleles at the same genetic loci to insulin levels and insulin sensitivity in 125 children of various racial mixtures. They found that the fasting insulin level varied directly and the degree of insulin sensitivity varied inversely with the number of alleles of African ancestry in these children. This genetic admixture analysis reveals the genetic underpinnings of the racial disparity in prevalence of T2DM beginning in childhood and shows that genetic background plays a primary role in increased susceptibility to T2DM in children with African ancestry.

Gestational Diabetes Mellitus (GDM)

GDM occurs in about 3 percent of pregnancies (Magee et al 1993). During pregnancy, affected women have high levels of plasma glucose. In response to high maternal plasma glucose, the islet cells of the fetal pancreas produce high levels of insulin, which often increase the babies' weight to between nine and 14 pounds. Such large babies are usually delivered by cesarean section. Because of their higher levels of insulin, these babies are at risk for neonatal hypoglycemia.

To ascertain the worldwide incidence of GDM and to assess the need for cesarean section, the ENGB is funding a study that will enroll 25,000 pregnant women at 15 sites in 11 countries. The protocol calls for participating obstetricians to be blinded to the glycemic status of pregnant women whose plasma glucose levels are below 105 mg/dL, in order to eliminate concerns for glycemic status from decisions about operative delivery. The results of this study will be available in 2007, and will help to improve the care of women with GDM by reducing both overtreatment and undertreatment of the condition on a worldwide basis.

OBESITY

In the 21st century, the future health of the nation is threatened by an epidemic of obesity that afflicts nearly one in every six children. Over the past 25 years, the prevalence of obesity in boys and girls ages six to 11, and in boys ages 12 to 17 tripled from 5 percent to 15 percent or more. The situation is particularly alarming among African American girls, ages six to 11 years old, whose obesity prevalence nearly quadrupled from 4.6 percent to 16.6 percent during this time frame.

Staff of the ENGB are involved in several major initiatives to reverse the increasing incidence of obesity, including meeting with congressional staff to discuss the content of the Improved Nutrition and Physical Activity Act (IMPACT), which passed the U.S. Senate in November 2003. ENGB staff also met with officers of the American Obesity Association to discuss the

public health crisis posed by obesity. Strategic meetings with the NIH director followed in early 2003, to devise a trans-NIH research plan to address the obesity epidemic, which led to the creation of the NIH Obesity Research Task Force. The Task Force is chaired by the directors of the NIDDK and the National Heart, Lung, and Blood Institute.

Major initiatives developed by the Task Force include:

- **Prevention and Treatment of Childhood Obesity in Primary Care Settings.** This RFA encourages investigators to test intervention programs set in primary care practices that aim to improve dietary and physical activity behaviors in children and adolescents. The RFA also encourages interventions to prevent further weight gain in children who are at risk for obesity, and to promote and maintain weight loss in children who are already obese. The NIH Obesity Research Task Force developed this RFA; nine Institutes and Centers support the RFA at a level of nearly $6 million per year.
- **Obesity and the Built Environment.** The purpose of this RFA is to improve understanding of the role the environment plays in causing and exacerbating obesity in the American population. A key goal of the RFA is to stimulate and test intervention strategies that encourage healthier lifestyles by making the built environment more appealing. For children, such interventions might include providing supervised playgrounds, bicycle and skating paths, safe sidewalks, and pedestrian overpasses in suburban neighborhoods. The NIH Obesity Research Task Force also developed this RFA; four Institutes and Centers support the RFA at a level of $4 million per year.

ENGB staff also worked with staff of the Institute of Medicine to provide research results for a report entitled *Preventing Childhood Obesity: Health in the Balance*, which was released at the National Press Club in September 2004. ENGB staff have also been instrumental within the DHHS in informing the national health objectives for nutritional and obesity goals in *Healthy People 2010*.

The Metabolic Syndrome

Obesity is part of a cluster of metabolic derangements called the metabolic syndrome, which often presages coronary heart disease, as well as T2DM. The metabolic syndrome has been detected in 25 percent of U.S. adults (NHANES III). Weiss et al (2004) found that obese children as young as four years old exhibit biomarkers for the metabolic syndrome, including elevated plasma triglycerides, glucose intolerance, and hypertension. These biomarkers are strongly associated with an increased risk of cardiovascular disease. The overall prevalence of the metabolic syndrome in this study was 50 percent in severely obese children, and 39 percent in moderately obese children.

Goodman et al (2004) applied adult criteria for the metabolic syndrome to 1,500 adolescents in greater Cincinnati to determine syndrome prevalence and found that 40 percent of obese teenagers met the World Health Organization (WHO) criteria for the metabolic syndrome. Girls were 25 percent more likely than boys to have the syndrome, and African American teens were 40 percent more likely than Caucasian adolescents to have the syndrome. Ascertaining the physiologic pathways and regulatory mechanisms that account for these sex and racial disparities are important future research endeavors for the Branch.

This research also demonstrated that each element of the metabolic syndrome worsens with increased obesity, which underscores the need to initiate interventions at an early age to decrease obesity in youth. These data also highlight the need for research on the progression of cardiovascular disease and T2DM in obese adolescents as they enter young adulthood.

Genetic Epidemiology of Obesity: The Muscatine Study

Although environmental and behavioral factors are the primary drivers of the epidemic of obesity that has engulfed the children of this country, genetic susceptibility also plays a critical role. This phenomenon is evident by observing the shift in obesity distribution among the population during the epidemic: the percentage of children who are morbidly obese has increased at a faster rate than that of any other group. Plainly, the fattest children are getting fatter. Evidence also suggests that these children have a genetic proclivity to store excess energy as fat.

In order to elucidate the genetic susceptibility of individuals at highest risk of obesity, ENGB-funded genetic epidemiologists at the University of Iowa have made remarkable strides in uncovering genetic predispositions to obesity. These investigators reported that 12 percent of markedly obese subjects carry a genetic polymorphism for the glucocorticoid receptor gene that confers an increased sensitivity to glucocorticoids. This polymorphism appears in only 4 percent of the general population of Muscatine (Tansey et al 2000). Genetic association analyses in the Muscatine population showed that leptin receptor-gene variants explain a significant proportion of obesity among members of the same family (Heo et al 2001).

These investigators also screened the coding region of the melanocortin receptor 4 (*MCR-4*) gene to identify mutations associated with autosomal dominant obesity. They reported a novel 15-base deletion that inhibits the binding of melanocyte-stimulating hormone to its receptor, thereby counteracting feeding inhibition (Tao et al 2003). This mutation is the first reported in *MCR-4* that causes loss of function due to the receptor's inability to bind to its ligand. The discovery may inform the development of new molecular entities that bind to the mutant receptor and can serve as substitute agonists. These genetic discoveries may also be used in high-throughput screening endeavors to identify susceptible children prior to the onset of morbid obesity.

Clinical Research Network in Non-Alcoholic Steatohepatitis (NASH)

NASH is the most prevalent liver disease in American children between ages 10 and 18 years old. It occurs most often in obese children at the time of puberty and, in severe cases, leads to hepatic fibrosis and cirrhosis. Little is known of the pathogenesis of or treatment for NASH, although prevention of obesity in childhood prevents NASH in adolescence. In fiscal year 2002, the NICHD joined the Clinical Research Network in NASH. The investigators in this Network recently initiated a clinical trial to explore the efficacy of using vitamin E and metformin in 180 obese children with NASH to reduce the impact of this serious complication of childhood obesity. The rationale for using vitamin E is to reduce the level of oxidant stress engendered by hepatic fat metabolism; the reason for including metformin is to increase hepatic sensitivity to insulin. The results of this trial should be available in 2008.

Planet Health: The Danger of Sedentary Behavior

Planet Health—an intervention curriculum that taught 1,200 sixth graders in Boston about the dangers of sedentary behavior—demonstrated that the prevalence of obesity in preadolescent girls was proportional to the number of hours they spent watching television. Those who completed the curriculum decreased television-watching time and experienced a dose-response effect on the reversal of the prevalence of obesity. The effect was most pronounced in African American girls, while the prevalence of obesity among boys remained the same before and after the intervention. These results demonstrate a striking sex-specific response to a behavioral intervention that invites further study (Gortmaker et al 1999). The investigators recently published the *Planet Health Manual of Operations*, which has stimulated others to start similar obesity prevention programs in 40 states.

Sedentary Behavior Research

Jeffrey et al (1982) noted that, between the ages of two and 17, children spend about 15,000 hours watching television, during which time they view about 350,000 commercials, many for snacks of high caloric density. Epstein et al (2002) showed that a 50-percent increase in television-watching time resulted in an increase in energy intake of about 250 kcal/day, and a decrease in energy expenditure of nearly 100 kcal/day; this shift results in a positive energy balance of 350 kcal/day, equivalent to a weight gain of nearly three pounds per month! These observations help to explain the relationship between watching television and the development of obesity in childhood. These investigators also designed a behavioral protocol in which sedentary youth are encouraged to be more physically active, a process that is reinforced with judicious access to television. Results of this intervention showed a 30-percent increase in physical activity and a more than 50-percent decrease in television watching compared to a control group. The reduction in television watching is also correlated with decreased body weight.

School-Based Interventions to Prevent Obesity

Recently, ENGB staff met with leaders of Action for Healthy Kids, an organization with a presence in all 50 states that encourages school-aged children to become more physically active. This meeting inspired the development of a PA promoting partnerships between school systems and academic institutions to foster the development of innovative school-based interventions to prevent childhood obesity. Schools seem to be ideal sites in which to implement such interventions because children spend about one-half of their waking lives in school.

Future Directions

The ENGB is pursuing a number of promising areas of research on obesity and precursors of adult diseases, including:

- **Determining when obesity becomes a disease rather than a condition.** The medical community has a strong interest in establishing criterion values of continuously distributed variables (i.e., BMI, blood pressure, plasma glucose, and serum lipids) that are associated with future morbidity and mortality. Developing predictive markers that can distinguish, with acceptable sensitivity and specificity, obese children who are at greater risk for future comorbidities from children at lesser risk is also important. Some, but not all, obese children will develop T2DM. Some will maintain remarkably high levels of plasma insulin for years in the face of profound insulin resistance, while others will succumb to T2DM in the second

decade of life, as a result of what is called "beta-cell exhaustion." Much remains to be learned about the molecular biology of beta-cell exhaustion. Research directed at what causes the beta cells in some children to fail in the face of insulin resistance may lead to new treatments that prevent or reverse the condition.

- **Improving the precision of defining obese phenotypes.**
  - Genotype-phenotype correlations are necessary in order to ascertain the risk of comorbidities in obese children. Single base-pair variations in genes can be ascertained by using molecular techniques of DNA analysis, but obese phenotypes can only be assessed by cruder measures, such as BMI and waist circumference. Research needs to focus on refining relevant phenotypes, as well as on families with extreme outliers. Studies of morbidly obese children and their lean siblings should be especially informative.
  - High-throughput screening tests are needed to detect informative gene products, such as the *MCR-4* receptor, so that genetically affected children can be identified before they become obese. In this way, investigators can demonstrate the mechanism by which these genes lead to obesity and may discover ways to prevent or reverse their effects.
- **Ascertaining the relationship between maternal obesity and congenital defects.** Epidemiologic studies have shown a robust statistical relationship between maternal obesity during pregnancy and neural tube defects, cardiac defects, and intestinal wall defects. Researchers have proposed several mechanisms to explain these associations, most involving aspects of glucose metabolism and levels of insulin and other growth factors. However, investigators have yet to identify a mechanism that causes these congenital defects in either humans or animal models. In view of the increasing number of obese women of childbearing age, it is important to elucidate the mechanistic link between maternal obesity and congenital defects in the offspring. Staff of the ENGB are working with the NIH Obesity Research Task Force to develop an RFA on the metabolic and developmental consequences of obesity during pregnancy.
- **Elucidating the molecular biology of exercise.** Epidemiological studies have shown the beneficial effects of exercise on cardiovascular risk factors. Further, sedentary behavior is a known risk factor for obesity, T2DM, hypertension, atherosclerosis, and osteoporosis. Physical activity ameliorates these conditions and may prevent their onset. However, the molecular mechanisms that link physical activity to disease prevention are currently unknown. Techniques to study differential gene expression and proteomics in sedentary versus active conditions will provide molecular clues for possible nutrient or pharmacologic interventions that can prevent such chronic diseases.
- **Establishing early endothelial pathology in children destined to be afflicted with early atherosclerosis.** The medical community needs to broaden its current emphasis on establishing risk factors that predict atherosclerosis later in life to ascertaining the early pathology of the arterial endothelial lining of children in their second decade of life. The endothelium is the vulnerable interface between the blood and the vascular tree. Key elements of this area of study include evaluating the sensitivity and specificity of non-invasive measures of carotid-intimal thickness and of brachial artery reactivity in adolescents from families with a strong history of coronary artery disease, and in those from families without such medical histories. Similarly, as a means to predict future disease, investigators should establish the value of measuring levels of pro-inflammatory and anti-inflammatory cytokines and chemokines in pediatric populations at high and low risk for early

atherosclerosis, and of measuring the levels of intercellular adhesion molecules and vascular adhesion molecules in these two groups of children.

BONE HEALTH AND OSTEOPOROSIS PREVENTION

Osteoporosis

Osteoporosis is a major health threat for 28 million Americans, 80 percent of whom are women. This preventable disorder originates in childhood and results from impaired acquisition of peak bone mass. Many children enter adulthood with skeletal systems compromised by poor nutrition and exercise habits. In addition, most teens fail to get the recommended daily allowance of minerals and vitamins crucial to bone health. For instance, the average teenage girl consumes only about 800 mg of calcium each day; her consumption falls 700 mg short of the amount of calcium recommended by the NIH Consensus Development Conference on Optimal Calcium Intake (1994). And, even small changes in bone mineral content and bone size early in life may have profound effects on fracture risk later in life.

To further understand these phenomena, the ENGB is funding six, randomized, controlled trials to test behavioral interventions aimed at increasing children's dietary calcium intake and physical activity. Two of the studies are school-based interventions that have study populations of 1,800 children each. These trials are designed to evaluate behavior modification techniques and social learning theory. The overall assumption of these studies is that lifestyle changes made during childhood will continue into adulthood and may lead to an increase in peak bone mass and a decreased incidence of osteoporosis.

Results indicate that increases in weight-bearing physical activity or calcium intake have positive effects on bone mass in children and adolescents (French 2000). Furthermore, the school-based intervention significantly increased physical activity and also served to prevent a decline in cardiovascular fitness. These findings are pertinent to bone health and also to the problem of diminished cardiovascular fitness that is common to sedentary adolescent girls and to obese children in general (Jamner 2004).

Growing bone is constantly remodeling itself, balancing new bone growth—laid down by cells called osteoblasts—against bone resorption by cells called osteoclasts. Clinical observations have indicated that some pharmaceutical agents can tip this balance: some toward more bone accretion, and others, especially corticosteroids, toward bone resorption. To plan new research directions in this area, the ENGB will co-sponsor a research-planning workshop with the American Society of Bone and Mineral Research entitled *Effects of Pharmacologic Agents on Bone Mineral Density in Childhood*. Participants will focus primarily on the effect of corticosteroids and bisphosphonates, such as alendronate and pamidronate, on bone accretion and resorption.

The Bone Mineral Density in Children Study (BMDCS)

The ability to diagnose and treat children who have chronic diseases that affect bone remains limited because the current age-specific norms for BMD are often inaccurate. The medical community requires standard reference data that consider skeletal maturation, volume, body size,

and pubertal factors, all of which seem to be more important determinants of BMD than chronological age.

In response to the need for pediatric BMD reference data, in 2001, the NICHD initiated the BMDCS, an effort that includes five clinical centers, all adhering to a common longitudinal observational protocol. Investigators conducted baseline evaluations of 1,554 boys and girls, ages six to 16 years. These children also took part in three consecutive annual evaluations, which included: dual-energy X-ray absorptiometry (DXA) of their lumbar spine, femur, and radius; bone age X-ray of the hand; and assessment of pubertal status, stadiometer height, weight, and physical activity level.

One of the BMDCS's key benefits is that it will establish whether DXA values obtained in early puberty predict BMD at sexual maturity. Furthermore, answers to nutrition and physical activity questionnaires may provide the data needed to ascertain optimal nutrient intake and exercise through childhood and adolescence, when bone mass is still actively increasing. Preliminary data show no leveling off of bone mineral accrual for the 19-year-olds, the oldest children in the study. This recently acquired knowledge extends the window of opportunity for interventions to improve bone health until late adolescence. These reference data will provide valuable guidance on monitoring bone health to children and young adults, their parents, and health care providers (see Appendix C for the BMDCS bibliography).

The Pennsylvania State University Young Women's Health Study

Despite the established benefits of regular physical activity, the prevalence of sedentary lifestyles among girls is increasing (Kimm et al 2002). Investigators followed 84 girls from age 12 to age 22 to assess the contributions of calcium intake and physical activity to total body bone mineral gain and peak hip BMD. They observed that sports-exercise scores correlated with increased hip BMD at age 18 years, but they observed no relationship between calcium intake during ages 12 years to 16 years and total body bone mineral gain or hip BMD at age 18 years. These investigators emphasized that a 0.05 g/cm^2 increase in hip-bone density represents a 50-percent reduction in osteoporotic fracture risk. In this study, a difference of 0.05 g/cm^2 in hip-bone density was associated with the amount of physical activity that distinguished a sedentary teenager from one who engaged in some form of exercise on a nearly daily basis. These longitudinal data (Petit et al 2004) demonstrate, for the first time, that femoral neck bone-bending strength continues to increase during young adulthood, despite static BMD measurements. This study indicates that bone strength adapts primarily to mechanical loading and underscores how important regular physical activity is for adolescent girls.

MATERNAL-FETAL ORIGINS OF ADULT DISEASE

Low birth weight babies are at risk for increased rates of long-term morbidity. In this country, about two-thirds of the babies who are born preterm are appropriate in size for their gestational age; however, the remaining one-third, or about 100,000 per year, are small for their gestational age because of intrauterine growth retardation (IUGR). Epidemiologic associations between IUGR and T2DM and cardiovascular disease later in life confer a new sense of urgency on this field of research.

Birth weight is known to vary directly with maternal pre-pregnancy weight for height and with maternal weight gain during pregnancy. Because these two factors account for only a portion of the variance in birth weight, investigators are searching for other contributors to birth weight, including vitamins, polyunsaturated fatty acids, and trans fatty acids. These studies aim to identify maternal diets that allow optimal fetal growth and infant development and that ensure a healthy life well beyond infancy.

Predictors of Newborn Blood Pressure: Project Viva

Elevated blood pressure in newborns may signal an increased risk for the development of cardiovascular disease later in life. In a study of 2,500 pregnant women and their offspring, Gillman et al (2004) reported that systolic blood pressure in newborns was approximately 0.8 mm Hg higher for each five-year increase in maternal age. Furthermore, high maternal blood pressure predicted increased newborn blood pressure. These researchers also reported that birth weight varied directly with newborn systolic blood pressure. Further research is required to understand whether high systolic blood pressure in the newborn predicts adult hypertension and its cardiovascular consequences.

Fetal Programming of Adult Disease

The intrauterine environment is a key factor in determining an individual's course of development into adult life. Imbalanced fetal programming has been associated with subfertility, cardiovascular disease, T2DM, and obesity. Low birth weight followed by rapid postnatal weight gain also confers a high risk for T2DM (Bhargava et al 2004) and for hypertension (Demerath et al 1999).

Evidence suggests that obesity and its unhealthy companions—insulin resistance, hypertension, and dyslipidemia—may be transmitted from mother to daughter. A prospective study of the offspring of mothers with GDM (Silverman et al 1998) found that the higher the mother's plasma glucose, the greater the insulin in fetal amniotic fluid. Higher amniotic fluid insulin levels, in turn, correlated with obesity and insulin resistance in the offspring during childhood and adolescence. This ominous finding implies a vicious cycle in which obesity and GDM are passed on from mother to daughter.

To augment research in this area, the ENGB published an RFA on the fetal origins of adult disease and funded six studies on this topic. Ward et al (2004) found that fetal response to stress *in utero* permanently alters the hypothalamic-pituitary-adrenal (HPA) axis. These investigators also reported that dysregulation of the HPA axis continues throughout life and engenders the metabolic and cardiovascular problems associated with low birth weight.

These investigators also studied the adult offspring of an unusual cohort of women—those who were urged to consume one pound of meat per day and to avoid carbohydrate-rich food during their last trimester of pregnancy. Herrick et al (2003) reported that cortisol concentrations in the offspring increased by 5.4 percent for each meat portion consumed by the mother each day. These finding provide the first human evidence that a high-protein diet during pregnancy programs life-long hypercortisolemia in offspring. High levels of this glucocorticoid engender insulin resistance and excessive deposition of visceral fat, increasing the risk for diabetes.

The Child Health and Development Study (CHDS)

The National Institute of Neurological Disorders and Stroke initiated the CHDS in 1959, as a companion to the Perinatal Collaborative Study. Since its inception, the CHDS has been instrumental in elucidating many aspects of public health that can be traced to maternal exposures during pregnancy. Under the leadership of Jacob Yerushalmy, the CHDS enrolled 20,000 women, early in their pregnancies, in order to study the effects of maternal infection, drugs, and other environmental exposures on fetal development and infant growth. The NICHD has funded the CHDS since 1974. Since then, the CHDS database has been computerized and is now available to investigators all over the world. Major portions of the CHDS data have been incorporated into textbooks on research design and statistical analysis. Recent notable findings include:

- Associations between maternal infections and schizophrenia in the offspring (Brown et al 2004);
- Impaired reproductive performance among the adult female offspring in relationship to organochlorine exposure of the index pregnancy (Cohn et al 2003);
- Effects of maternal exposure to alcohol, nicotine, and methylxanthines during pregnancy on the daughters' age of menarche (Windham et al 2004); and
- Relationship of maternal serum-alpha fetoprotein levels to breast cancer later in life (Richardson et al 2000).

ENDOCRINOLOGY

HUMAN GROWTH HORMONE (HGH)

The industrial production of hGH has greatly increased the supply of this potent, 191-amino-acid polypeptide. The increased availability of hGH makes possible therapy for children who are not hGH deficient, but who are two or more standard deviations below mean height for age. However, treating these children has far-reaching social and economic ramifications. In the United States, the number of children eligible for hGH treatment ranges from 11,000—if strict criteria for hGH deficiency are applied—to 1.3 million—if all those with heights below the third percentile are candidates. If the less-stringent criteria became the standard of care, the respective cost of hGH therapy would jump from $155 million to $20 billion per year (Cuttler et al 1996). So far, pediatricians in the United States have shown welcome restraint in prescribing hGH for non-approved indications (Finkelstein et al 1998).

The Branch has been at the forefront of efforts to ascertain indications for the use of hGH in treating short children. ENGB staff worked with the Developmental Endocrinology Branch, within the NICHD Division of Intramural Research, to design a randomized, placebo-controlled clinical trial testing the efficacy of hGH in short children who appear to have sufficient hGH on provocative testing (Gertner 1988). Results of this landmark trial showed increases of between 3 cm and 5 cm in final height among the children who received hGH (Leschek et al 2004).

MOLECULAR BIOLOGY OF hGH AND ITS RECEPTOR

The ENGB has made a concerted effort to emphasize studies on the molecular basis of growth in order to exploit recent developments in molecular biology and bioinformatics. This programmatic shift has been rewarded by a series of stunning discoveries. In examining the co-evolution of hGH and its receptor protein, Li et al (2001) analyzed tens of thousands of nucleic acid sequences in the human genome. They identified 43,195 genetic sequences that contained the elements necessary to transcribe messenger RNA (mRNA) into a template for assembling amino acids into proteins. However, only 15,337 of these genes code for known proteins. The remaining 27,858 unknown genes code for proteins *that have yet to be isolated and described*. These observations indicate that the number of human genes is much lower than previously thought; until recently, scientists believed the number to be in the range of 100,000.

In related research, Nekrutenko and Li (2001) examined the function of the more than 4 million long, repetitive sequences of DNA, called transposable elements, in the human genome. Transposable elements possess a protean ability to move around the genome. Most of these moves are inconsequential because they do not affect the small portion of the genome that codes for proteins. However, occasionally transposable elements insinuate themselves within coding regions and cause genetic disease, such as factor VII deficiency hemophilia.

These investigators discovered that about 1,200 human genes contain transposable elements within their coding regions. In some genes, these embedded elements code for portions of proteins that are necessary for proper enzyme function, as is the case for hematopoietic progenitor kinase and for a DNA oxidative repair enzyme. These exceptional findings have evolutionary implications, too. Insertion of transposable elements accelerates the evolution of genes and drives species divergence. Occasionally, insertion of transposable elements increases the functional versatility of genes by providing the code for alternative proteins within the same gene. This illuminating discovery paves the way for the use of transposable elements in genetic medicine, in that researchers may be able to tailor genes to code for novel proteins by inserting transposable elements at specific sites in the gene's coding sequence. Such "designer" proteins may prove useful as therapeutic agents.

CONGENITAL ADRENAL HYPERPLASIA (CAH) AND OTHER DEFECTS OF STEROID METABOLISM IN CHILDREN

CAH is a family of genetic disorders caused by mutations in the genes that code for adrenal enzymes, which are essential for cortisol biosynthesis. Recent molecular advances have elucidated the genetic basis for the phenotypic variability in CAH and have provided a means for genotyping relatives of index patients. These advances have permitted prenatal genotype ascertainment in fetuses at risk for the disorder and have helped define hormonal criteria for the varying spectrum of CAH disorders. Biochemical advances have simultaneously aided the diagnosis and therapeutic monitoring of CAH patients.

New et al (2001) reported on their 15-year experience with prenatal diagnosis in 532 pregnancies, of which 281 were treated for CAH prenatally with dexamethasone. This novel fetal therapy prevents the overproduction of masculinizing steroid precursors by the adrenal gland and results in the birth of girl babies with normal genitalia, despite their defective alleles for genes encoding 21-hydroxylase or 11 beta-hydroxylase. This prenatal therapy prevents or minimizes virilizing sequelae in the majority of affected girls. Thus, prenatal diagnosis and proper prenatal treatment of CAH can reduce or eliminate virilization and decrease the likelihood of genital ambiguity, genital surgery, and sex misassignment.

In more than two-thirds of affected neonates, newborn screening for CAH has also contributed to the prevention of morbidity from delayed diagnosis. Current treatment methods, however, may not be optimal for achieving normal genetic height and appropriate weight in CAH patients; therefore, researchers are exploring more effective approaches to CAH therapy. Severe short stature in adult patients with CAH remains a significant problem. Quintos et al (2001) showed that treatment with hGH alone, or with a combination of hGH and analogues of gonadotropin-releasing hormone (GnRH), improves growth rate and height prediction in CAH patients.

Dr. New and colleagues have also discovered eight functionally important point mutations of the gene that encodes 21-hydroxylase, as well as several gene deletions and gene conversions at the *CYP21* and the *CYP21Pseudogene* loci on the short arm of chromosome 6. These mutated alleles engender various levels of 21-hydroxylase activity in affected individuals and may be present in various combinations, a condition known as compound heterozygosity. CAH-affected individuals may suffer life-threatening degrees of salt loss, virilization with severe hypertension, or obesity, hirsutism, disfiguring acne, and infertility. Combinations of faulty alleles and the variety of enzyme activities associated with these mutations explain the spectrum of clinical CAH phenotypes.

The successful explanation of how a single-gene defect could engender such a wide spectrum of clinical presentations stands as a model of how molecular biology can inform clinical observations. In the course of these genotype-phenotype explorations, Dr. New showed that non-classical CAH is one of the most common autosomal-recessive genetic disorders known, occurring in about one out of every 30 Ashkenazi Jews, and in one in 100 individuals in a mixed Caucasian population. Thus, the non-classical allele of the 21-hydroxylase gene may be the most common autosomal-recessive gene in human populations.

Carbunaru et al (2004) are examining rare forms of CAH, such as inherited 3beta-hydroxysteroid dehydrogenase (3beta-HSD) deficiency, to determine the phenotypic correlates of severe and mild forms of the disease and to explore the potential relationship of 3beta-HSD deficiency to polycystic ovary syndrome, the symptoms of which include hirsutism, menstrual disorders, and infertility. Investigators have recently pursued newly proposed hormonal criteria to accurately predict inherited 3beta-HSD deficiency.

Cerame and New (2000) are also exploring genotype-phenotype correlations in two inherited endocrine disorders responsible for hormonal hypertension in children: a) 11beta-hydroxylase deficiency, a condition that results from an autosomal-recessive defect of the protein-encoding gene *CYP11B1*; and b) apparent mineralocorticoid excess (AME), a potentially fatal genetic disorder that causes juvenile hypertension and prenatal and postnatal growth failure. AME is

characterized by low to undetectable levels of serum potassium, renin, and aldosterone. Mutations in the coding region of AME cause a deficiency of 11beta-hydroxysteroid dehydrogenase type 2 (HDS11B2), an adrenal enzyme necessary for converting the potent steroid cortisol into its less active form cortisone. This group of investigators discovered AME, elucidated its pathophysiology, and was first to use a mineralocorticoid receptor antagonist to treat the condition.

In evaluating a child with AME, Lin-Su et al (2004) recently reported a novel mutation of the *HSD11B2* gene. The affected nine-year-old girl had a blood pressure of 225/120 mm Hg, which was engendered by excessively high levels of cortisol. These high levels of cortisol, in turn, activated the renal mineralocorticoid receptors, driving her blood pressure to dangerously high levels.

New et al (2001) also discovered a previously unreported condition, which they named multiple steroid resistance syndrome. They made this discovery when evaluating a 14-year-old girl from the Iroquois Nation for possible AME. Despite high cortisol levels and elevated levels of adrenal androgens, the girl exhibited no features typical of excessively high levels of steroids, such as truncal obesity, hyperglycemia, and masculinization. The patient's sister had similar features. Both girls demonstrated resistance to exogenously administered glucocorticoids and mineralocorticoids. The pathogenesis of this unusual condition may involve defects in co-activators that are necessary for proper steroid receptor-gene expression.

NEUROENDOCRINOLOGY

Intersex Disorders

Some of the most vexing problems seen by pediatric endocrinologists are intersex conditions, which are characterized by ambiguous genitalia at birth, or by a dissonance between genetic sex and genital appearance. New techniques in molecular biology are shedding light on the genetic and developmental origins of intersex conditions, including an unusual form of sex reversal (Jordan et al 2003). To address this disturbing and psychosocially challenging issue, the ENGB, in conjunction with the NICHD Child Development and Behavior Branch and the North American Task Force on Intersex, organized a research-planning workshop on evidence-based management of intersex conditions. The frank deliberations among the pediatric endocrinologists, psychologists, and pediatric urologists present produced a unique research agenda, recently published in *The Endocrinologist* (Meyer-Bahlburg and Blizzard 2004). One important outcome of the workshop was the establishment of an NICHD Network on Psychosocial Aspects of Sexual Differentiation. In addition, the ENGB is funding new analyses of two, large databases on intersex children. The analyses include evaluations of gender assignment, hormonal therapy, and genital reconstructive surgery. Results of these analyses should be available soon and will be shared with the members of the Network.

The Onset of Puberty

Precocious puberty is a problem commonly encountered by pediatric endocrinologists. The majority of clinical problems with features of precocious puberty are benign normal variants, with a low incidence of endocrine pathology. Less commonly encountered are disorders of

delayed puberty. Recently, there has been much controversy over the age of onset of puberty in normal children and the risk of missing pathology if recently proposed, revised-age guidelines for referring patients are put in practice. Ojeda et al (2003) have elucidated the complex neuroendocrine mechanisms involved in the onset of puberty. They have demonstrated that the pubertal activation of GnRH secretion is set in motion by changes in trans-synaptic communication and the activation of glia-to-neuron signaling pathways. The identification of genes that control this cascade, as well as the identification of molecules involved in the rearrangement of neuronal and glial communication during puberty, have provided vital insights into the mechanisms underlying sexual maturation.

Dissen et al (2002) have shown that nerve growth factor, a member of a family of growth factors known as the neurotrophins (NTs), is required for the growth of primordial ovarian follicles, a process that occurs independently of the endocrine system. The presence of intrinsic neurons in the ovary stimulated these investigators to elucidate the functions these neurons may have in the regulation of ovarian physiology. The researchers found that NTs play a role in the regulation of two different maturational periods that are critical for the acquisition of female reproductive function: early follicular development and ovulation. The intrinsic neurons in the ovary appear to regulate common ovarian functions. A greater knowledge of this neuronal regulation should expand understanding of ovarian pathologies.

Basic Fibroblast Growth Factor (bFGF) and Brain Neurogenesis

Until recently, scientists considered the number of cerebral neurons to be fixed at birth and to be unresponsive to environmental signals later in life. However, Wagner et al (1999) found that bFGF stimulated neurogenesis in the brains of newborn rats. They also found that bFGF stimulated cerebral DNA synthesis in older animals, indicating the persistence of bFGF-responsive cells into adulthood. These observations suggest that bFGF regulates ongoing neurogenesis and may provide a new approach for treating damaged brains during development and into adulthood.

Bone Marrow Stem Cells: A Self-Repair Kit?

Marrow stromal cells (MSCs) are a subclass of bone marrow stem cells. Woodbury et al (2001) found that human-cultured MSCs can be induced to differentiate into neurons by exposing them to antioxidants and bFGF. MSCs offer important advantages over other stem cells because they are readily accessible and provide a renewable cell population. Autologous transplantation overcomes the ethical and immunologic concerns associated with use of fetal tissue transplants.

Recently, Munoz-Elias (2004) successfully transplanted adult rat MSCs into a rat brain embryos *in utero*. After transplantation, MSCs not only differentiated and migrated in the embryonic brain, but also survived and functioned. Importantly, the newly developed neurons expressed the proper morphology and physiology of the brain region to which they migrated. Human MSCs may eventually be used to treat congenital neurologic disorders *in utero*, newborn brain injuries, and neurodegenerative disorders.

Future Directions

The highly informative exploration of genotypes in the spectrum of CAH phenotypes stands as a model for the elucidation of phenotypes in other conditions with a wide variety of clinical

presentations, such as short stature, hypoparathyroidism, and autoimmune polyglandular failure. Techniques of molecular biology can now be applied to improve our understanding of hormone-receptor interactions and the cascade of intracellular events that lead to altered gene expression in such endocrine deficiency syndromes. The development of high-throughput molecular-genetic screening techniques will be encouraged in order to improve diagnostic precision in pediatric endocrine clinics that deal with puzzling cases much of the time.

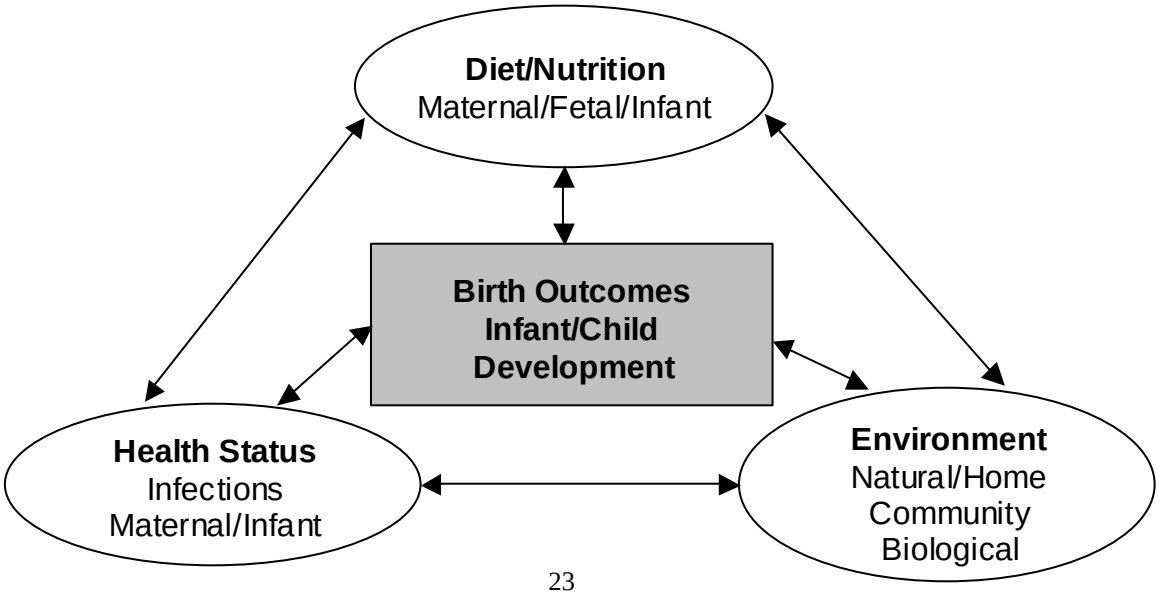
The development and function of the neuroendocrine system in preterm infants needs to be further explored. The nascent field of neonatal endocrinology needs to address the neuroendocrine system's ability to respond to the stresses of extrauterine life. The converse question of how the stress of extrauterine life permanently alters the developing endocrine system needs to be addressed as well. The functioning of the endocrine system in cases of failure to thrive should also be explored, especially in regard to the development of appropriate hormone replacement in conjunction with nutritional support.

The ENGB will encourage further studies of the interactions of the three great messenger systems of the body: the endocrine, immune, and neural systems. The techniques of molecular biology, when applied to these interactions, should be especially informative in regard to the function of early neural input into the development of the endocrine organs. Advanced techniques of proteomics, such as laser desorption-ionization coupled with mass spectrometry, should elucidate early malfunction of the immune surveillance system in autoimmune endocrinopathies. These techniques can detect the presence of evanescent cytokines and chemokines in femtomolar or even attomolar quantities.

NUTRITION

Nutrition is linked to all aspects of human biology and health. The figure below shows how diet interacts with the environment to determine the health status of women, infants, and children.

Interaction between Nutrition, Environment, and Health Outcomes



This conceptual framework applies to studies ranging from the identification of bioactive components in human milk, to the impact of micronutrients on growth and development. A strength of the ENGB nutrition research portfolio is that it explores nutritional variables in both domestic and international contexts.

MATERNAL-FETAL NUTRITION

A fruitful area of research activity involves the study of how the fetal environment determines the incidence of obesity, diabetes, and cardiovascular disease in adulthood. Several ENGB projects focus on the impact of fatty-acid metabolism on fetal and postnatal development. Oken et al (2004) examined the effects seafood intake—an indirect measure of maternal dietary long-chain polyunsaturated fatty acid (LCPUFA) intake—on fetal growth and birth outcomes. They founded no association between seafood intake and either length of gestation or risk of preterm birth. However, they did find an association between high seafood consumption and IUGR. This finding is of public health significance in light of the growing perception about the need for higher LCPUFA consumption.

The epidemics of obesity and T2DM in adults have also raised concerns about the impact of these conditions on fetal growth and birth outcomes. Shen et al (2002; 2003) have explored the relationship among insulin, insulin-like growth factor-1 (IGF-1), and fetal metabolism and growth in a sheep model. The combination of insulin and IGF-1 enhances growth in this model by inhibiting proteolysis to a greater degree than either hormone acting alone. Understanding these relations may help to prevent some of the untoward effects of maternal obesity and fetal overgrowth.

Future Directions

Among the important aspects of the obesity epidemic is the potential impact of maternal over- and under-nutrition on fetal growth and birth outcomes. Worldwide, under-nutrition is known to be a significant contributor to low birth weight (infants born weighing less than 2,500 grams), but recent evidence indicates that over-nutrition and maternal obesity also have a deleterious impact on infant health. The ENGB will explore these and other issues in future programmatic activities.

LACTATION AND MILK COMPOSITION

The ENGB supports studies on the processes by which the mammary gland changes from a ductal network, to a secretory organ capable of copious milk secretion. Of critical importance is the mechanism(s) by which nutrients get into human milk and the processes by which lipids are formed. This research has made a significant contribution to understanding the physiology of the mammary gland, and to the health of both nursing infants and their mothers (Rudolph et al 2003).

In view of global recommendations about the duration of exclusive breastfeeding and the timing of introduction of complementary foods, the ENGB is interested in ascertaining nutrients that might be limiting in human milk. In this regard, the nutrient that has received most attention is iron. ENGB-supported investigators are leading the effort to understand the adequacy of iron for infants during the course of extended breastfeeding. Additional studies are in progress to test the hypothesis that breastfed infants older than six months of age are at risk for iron deficiency in the absence of a supplemental dietary iron source. This work will include a delineation of the extent of iron deficiency and the time course of iron status in breastfed infants.

An important aspect of understanding those factors that contribute to adequate iron status is an appreciation of the factors that contribute to iron balance and subsequent iron requirements, particularly during growth. Fomon et al (in press) reported on stable isotope studies in infants from age four months to 26 months. These investigators found that iron stores were low throughout the study and decreased significantly from 13 months of age to 26 months of age, suggesting that iron absorption from the diet was inadequate to maintain or increase iron nutritional status. These findings are particularly important in the context of extended breastfeeding; they will also help inform the discussion about appropriate complementary foods for infants during extended breastfeeding, i.e., beyond six months.

Antimicrobial Agents in Human Milk: A New Class of Antibiotics?

Throughout the world, the majority of the 10 million children younger than age five who die every year succumb to severe diarrhea and dehydration. Worldwide, rotavirus is the most common cause of diarrhea in infants and young children, and this virus causes 50 percent of gastroenteritis cases in the United States. In this country, the most common cause of bacterial diarrhea is *Campylobacter jejuni*, which initiates disease by binding to intestinal cell surfaces.

In a concerted effort over the past decade, Morrow et al (2004) have elucidated the function of certain non-nutritive components of human milk, called oligosaccharides—the third most abundant constituent of human milk, after lactose and lipids. Investigators found that oligosaccharides bind to enteric bacteria and viruses, thus preventing these pathogens from infecting the cells that line the infant intestine. In a series of landmark studies, these investigators found that oligosaccharides inhibit the toxic effects of enteropathogenic *E. coli*, and inhibit infection by *C. jejuni* (Ruiz-Palacios et al 2003) and by caliciviruses, one of which is the Norwalk virus that incapacitates thousands of cruise-ship voyagers every year (Jiang et al 2004).

These researchers have also shown that lactoferrin significantly decreases the invasiveness of *Shigella flexneri*, another enterobacteria, by degrading bacterial proteins called invasion-plasmid antigens. Further, they found that lactadherin prevents symptomatic rotavirus infection in breastfed infants by binding to rotaviral particles and inhibiting their replication. These results may lead to the use of lactoferrin and lactadherin as antibiotics or as prophylactic agents against intestinal pathogens for both infants and adults.

This ENGB-supported work signals the advent of a new class of antimicrobial agents to prevent and treat bacterial and viral infections. An important advantage of developing synthetic oligosaccharides and glycoproteins as antibiotics is that, because they block receptor binding

rather than interfering with protein synthesis and bacterial replication, these compounds do not induce bacterial resistance, an increasingly problematic aspect of antibiotic usage.

Future Directions

- The discovery of the antimicrobial effects of oligosaccharides and glycoproteins in human milk marks a new departure in the development of antibiotics. ENGB staff will encourage investigators to produce these agents synthetically, with the aim of testing them as prophylactic and curative antibiotics.
- Questions persist about how to achieve optimal infant nutrition. A key issue in this area is the timing and composition of complementary feeding. Determining the importance and duration of exclusive breastfeeding is a priority in terms of both the health of the infant and the needs of the mother. The Branch will encourage studies exploring the factors that influence the composition of human milk, particularly during extended breastfeeding. The ENGB will continue to stimulate research in this important area, which has both domestic and global health implications.

INFANT NUTRITION: CLINICAL IMPLICATIONS

The LCPUFAs have emerged as important components of clinical interest for infant nutrition. Birch et al (2002) are exploring the role of docosahexaenoic acid (DHA) in visual development of term infants. These researchers have reported significant positive associations between DHA intake and maturation of visual function. Questions about the source of and requirements for DHA for these infants remain topics of high interest. This research has also stimulated interest in the role of LCPUFAs in normal neurological development and in best practices for feeding term infants throughout the first year of life (Hoffman et al 2003; 2004).

In attempting to explain LCPUFAs' effects on development, Lapillone et al (2004) explored the effect of LCPUFAs on gene expression. They reported that LCPUFAs play an important role in the regulation of genes that affect cell function, development, and maturation.

Nutrition in Preterm Infants

Even though preterm infants need feeding strategies that mimic *in utero* growth rates for both brain and body, researchers have yet to develop optimal feeding strategies for this population. In many cases, feeding strategies are conservative in an attempt to avoid inducing NEC. Many preterm, very low birth weight infants (those weighing less than 1,500 grams) rely on total parenteral nutrition (TPN) to receive nutrients for growth and development. These infants have a large brain-to-body ratio, which increases their glucose demands because glucose is the primary source of energy for the brain. However, neonatologists run a high risk of inducing hyperglycemia simply by increasing the glucose concentration of the TPN solution. Sunehag (2003) has shown that increasing the lipid content of TPN can supply the necessary energy to the brain, while still maintaining normoglycemia in these infants.

Agus and Jaksic (2002) explored infants' protein catabolic response to severe illnesses that dangerously deplete lean body mass. In order to understand the needs of these sick infants, this group of researchers has examined endocrine- and cytokine-mediated responses that contribute

to the adverse effects of severe illness. They observed that infusions of insulin temper this catabolic response, a discovery that has important implications for the care of critically ill infants (Agus et al 2004) and adults.

Poindexter et al (2001) have been evaluating the importance of maintaining nitrogen balance in preterm infants, with a primary focus on factors that affect protein accretion in extremely low birth weight infants (those weighing less than 1,000 grams). This research found that administering large amounts of essential amino acids to preterm infants did not protect their fragile bodies against protein degradation. Results indicate that preterm infants develop an adaptive response leading to long-term changes in protein and energy metabolism, insulin sensitivity, and endothelial function, which affect growth and development and also increase the risk for obesity, diabetes, and cardiovascular disease later in life.

Future Directions

Preterm birth interrupts the placental supply of nutrients essential for normal growth and neurological development. A central research question is how best to overcome the consequences of that interruption. It appears that there is a critical period of maximal accretion of protein for fetal growth that, if interrupted by preterm birth, has adverse health consequences. The goal of future studies will be to develop feeding strategies for the preterm infant that will protect against these adverse effects, while providing an opportunity for optimal growth and development.

FOOD INTAKE REGULATION AND ANTECEDENTS OF FOOD BEHAVIOR

The ability to devise interventions that will improve the health of infants and children depends on understanding both biological and the sociocultural contexts of the interventions. Studies of how food intake is regulated, from both biological and environmental perspectives, continue to be a research priority for the ENGB.

From the biological perspective, Tracy et al (2004) conducted a series of studies to explore neural pathways between the brain and the gastrointestinal tract that influence appetitive behavior. One of the hypotheses driving this work is that a degradation of the ability to use certain sensory cues to predict the caloric consequences of intake, and the uncoupling of these signals may contribute to overeating and weight gain. The implications of this research for clinical management of obesity are important.

In an environmental context, evidence suggests that the hedonic response to food is an important component for entraining food preferences and lifetime food habits. Mennella et al (2004) explored the ontogeny of flavor learning in infants. Based on this research, it seems that flavor preference is developed on the basis of timing and exposure and has a significant impact on food acceptability later in life. These studies and their results have important implications for early infant-feeding practices and for palatability of children's medications.

In addition, Shunk and Birch (2004) described behaviors in five-year-old children that predict eating disorders and concerns about weight gain and body image later in life. Health care

providers can use these results to identify vulnerabilities and outcomes associated with maladaptive eating behavior that begins at an early age.

Future Directions

Efforts to predict adverse outcomes of maladaptive food behavior are an essential component of evidence-based strategies to address obesity and other diet-related public health concerns. One area that warrants increased attention is understanding the social and cultural factors that contribute to healthful eating habits, particularly within the context of health disparities. The rising use of dietary supplements to enhance physical and mental performance and to improve health of infants and children is also an area of research interest within this portfolio.

IMPACT OF MICRONUTRIENTS ON HEALTH

The ENGB is actively engaged in projects that examine the importance of micronutrients in maternal and child health. Justifying interventions to ameliorate micronutrient insufficiency requires an evidence base that has a biological basis, and that is couched in the cultural and demographic context of the people these interventions are intended to serve.

In most cases, the impetus for exploring the effects of individual micronutrients in the developing world is an assumption that a given micronutrient plays a role in the etiology of a major public health problem, such as anemia or malaria. Justifying these interventions begins by documenting the impact of the micronutrient on health and establishing that a population-wide deficiency exists. Once that evidence is documented, researchers can design a specific intervention. ENGB-supported investigators have led the efforts to advance appreciation of the functional relevance of micronutrient insufficiency and to conduct clinical trials that assess the efficacy of nutritional interventions in resource-limited settings.

The Institute of Nutrition of Central America and Panama (INCAP) Longitudinal Study, which involves four villages in Guatemala, is a seminal study of the beneficial impact of a simple dietary intervention on child health. Stein et al (2004) reported a positive impact on the linear growth of subsequent generations of infants who were born to supplemented mothers. Li et al (2003; 2004) found improved adult educational achievement consequent to remote nutritional intervention. An encouraging finding is that both maternal and child nutritional supplements were associated with lower fasting glucose concentrations later in life (Conlisk et al 2004). This multi-generational study reinforces the importance of early nutrition in long-term health outcomes.

Iron Supplementation

Iron deficiency affects more than two billion people worldwide (Ramakrishnan et al 2002a). Investigators identified factors that contribute to the risk for iron deficiency in the U.S. population. These investigators reported that diminished iron stores in women were caused less by low iron intake than by factors that influenced iron bioavailability, such as vitamin C intake.

Data from iron fortification and supplementation programs indicate that iron repletion and increased iron stores may have negative effect on health. Studies have shown an association

between cardiovascular risk and iron stores in men in the industrialized world. To explore the possibility of a similar association in women of reproductive age, Dr. Ramakrishnan analyzed national U.S. data and reported a similar association in these women, especially between aberrant glucose and lipid metabolism and iron status (Ramakrishnan et al 2002b).

Zinc Supplementation

The understanding of zinc's importance to human nutrition and health has expanded greatly since Prasad first reported hypogonadism and growth stunting in zinc-deficient children in 1963. ENGB-funded investigators have been at the forefront of efforts to determine the biology and the efficacy of zinc supplementation in the context of global health.

Zinc plays key roles in gene expression, immune function, hormonal regulation, and growth. However, approximately 30 percent of pregnant women suffer from inadequate amounts of dietary zinc (Merialdi et al 2004). Researchers examined the effects of 25 mg/day maternal zinc supplementation on fetal bone growth and fetal heart rate. They found a significant increase in fetal femur length among the zinc-supplemented group. They also provided compelling evidence for the critical role of zinc on fetal heart development. Their results showed that zinc-supplemented mothers gave birth to babies with lower fetal heart rates and greater heart rate variability, signifying greater adaptability of the newborn heart than was previously thought. The conclusion that long-bone growth *in utero* can be enhanced by maternal zinc supplementation is a novel finding in humans and provides further evidence of the effect of zinc on growth and development.

Researchers also pooled and analyzed data from 10 trials of zinc supplementation ranging from 5 mg per day to 10 mg per day given to children in developing countries. This analysis revealed a 25-percent reduction in the incidence of diarrhea and a 41-percent reduction in the incidence of pneumonia. The effectiveness of zinc as a single-nutrient supplement is striking; its effect on pneumonia prevention accounts for the entire estimated contribution of malnutrition as a risk factor. In normalizing the function of cells in multiple tissues, zinc supplementation enhances a child's ability to combat entire disease states, not just single infectious organisms. These remarkable results imply that zinc supplementation may prove more economical than vaccines when directed against specific organisms (Bhutta et al 1999).

Future Directions

A growing body of evidence indicates that supplementation with single micronutrients, e.g., vitamin A, vitamin E, and iron, can have deleterious consequences in nutrient-replete subjects, or in those infected with HIV. The ENGB is planning a series of workshops to elucidate the mechanisms and predictors of these potential adverse effects for mothers, infants, and children, particularly those that occur in resource-limited settings. The ENGB is dedicated to developing a credible process for translating research data into evidence-based programs for successful nutritional interventions.

In specific cases, such as with vitamin D, a better understanding of the full range of functions affected by micronutrients and of the long-term impact of early problems with nutrient status is needed before researchers can make recommendations regarding its use. Such questions can be

considered not only within the context of the fetal/infant origins of adult disease hypothesis, but also on an individual basis as evidence warrants.

Studies are also needed to evaluate the role of Western diets in predisposing persons to diabetes and the metabolic syndrome, globally, within the context of the nutritional transition that occurs in many countries as an unwelcome consequence of economic development.

The role of nutrition in the susceptibility to and natural history and treatment of HIV/AIDS has emerged as a significant public health concern, especially in resource-limited settings. In response to the growing interest in finding evidence-based strategies to incorporate food and nutrition into all aspects of prevention, care, and treatment of HIV/AIDS, ENGB program staff provides technical input on the membership of the WHO Technical Advisory Group on Nutrition and HIV/AIDS. In addition to a technical report that will provide a comprehensive review of the extant data and guidelines supported by evidence, the Advisory Group will organize a consultation in Durban, South Africa, intended to engage the nations and agencies involved in addressing HIV/AIDS and its impact on people in sub-Saharan Africa. In addition, the ENGB, in partnership with the Pediatric, Adolescent, and Maternal AIDS Branch of the NICHD's CRMC has published a PA specifically focused on studies of the relationship between nutrition and HIV/AIDS in women, infants, and children.

NECROTIZING ENTEROCOLITIS (NEC)

NEC is a devastating gastrointestinal disease that strikes about one in 10 preterm infants who are born weighing less than 1,500 grams. Affected infants who escape death are often left with morbid sequelae, such as intestinal strictures, short gut syndrome, and malabsorption. The etiology of NEC remains unclear, but two commonly reported risk factors are being born preterm and enteral feeding. Elevated serum levels of factors involved in the inflammatory process may also play a role in the morphological changes seen in NEC.

Claud et al (2004) reported high levels of the inflammatory cytokine IL-8 in NEC. They also found that immature enterocytes have decreased levels of *IκB* gene expression; furthermore, increasing the level of *IκB* expression in the immature enterocytes dampened the over-secretion of IL-8 in the immature intestine. This previously undescribed association of *IκB* to NEC adds to the understanding of the pathogenesis of NEC and may lead to new treatment options for infants afflicted with the disorder. In addition, decreased *IκB* expression could be used as a marker indicating increased risk of NEC.

Epidermal Growth Factor (EGF): A New Treatment for NEC?

Although maternal milk plays a protective role against NEC in both animals and humans, currently no known preventive therapy for NEC exists. To elucidate how maternal milk reduces the risk of NEC, Dvorak et al (2002) hypothesized that EGF, a constituent of milk, might be the preventive factor. These investigators fed milk with and without EGF to newborn rats and then induced NEC by exposing the animals to hypoxia and cold stress. EGF supplementation reduced the incidence of NEC from 81 percent to 30 percent in the animals.

These findings seem to warrant implementing a protocol in preterm human infants, in which they could be randomized to formula with and without EGF in order to ascertain whether the compound similarly reduces the incidence of NEC in humans. These findings also imply that EGF could stimulate intestinal repair processes in other gastrointestinal disorders, such as ulcerative colitis.

GROWTH AND DEVELOPMENT

THE FELS LONGITUDINAL STUDY OF PHYSICAL GROWTH AND DEVELOPMENT

The Fels Longitudinal Study is the oldest and largest study of growth and body composition in the world. Arthur Morgan, president of Antioch College, initiated the multidisciplinary study in 1929, along with Lester W. Sontag, to find out why people differ from each other in these aspects. The Fels Study includes serial growth data on 1,400 individuals whose height, weight, body composition, bone density, plasma lipids, and lipoproteins have been carefully measured at regular intervals from birth through adulthood.

Data generated by this study form the basis for the North American Standard Tables of Height and Weight, which are used to record and monitor children's physical growth, as well as to predict adult height. With more than 100 million charts already distributed, courtesy of Ross Laboratories, physicians can compare their patients to the Fels population to make judgments about an individual's body size and proportions. The Centers for Disease Control and Prevention recently incorporated Fels Study data into its growth charts; the WHO also adopted these data to monitor children's growth and nutritional status all over the world. Researchers have also used these data to develop additional tables to allow the measured height of a child to be adjusted for parental stature. The pioneering work of the Fels Study investigators established standards for bone growth according to chronological age. These data are now being enhanced by results from the BMDCS, which provide an expanded understanding of bone accretion during the various stages of pubertal development.

Scientists have also used Fels Study data to generate charts of normal bone age based on 4-million observations of knee, hand, and wrist radiographs. These charts are in widespread use by pediatric endocrinologists, radiologists, and other health care providers who deal with problems of growth retardation or inappropriate bone age acceleration, as in cases of precocious puberty. These data also allow researchers to estimate the heritability of skeletal age at annual increments, from age three to age 15, and to determine the genetic and environmental correlations between skeletal age estimates across this age range.

Recently, researchers analyzed serial data on the BMI and blood pressure of the Fels Study participants from birth to adulthood, to prospectively test Barker's hypothesis about fetal origins of adult disease. The data confirmed Barker's observation of higher systolic blood pressure in males of low birth weight. However, a 5-kilogram increase in BMI after age 18, which was seen only in the low-birth-weight group, could account for the blood pressure increment in the low

birth weight group (Demerath et al 1999). This observation underscores the statistical power inherent in the Fels Study data set. Fels Study researchers have also used their extensive database to study the onset of cardiovascular risk factors in boys and girls, and to establish criterion values for children that predict the onset of the metabolic syndrome later in life (Sun et al 2004).

PEDIATRIC PHARMACOLOGY

THE PEDIATRIC PHARMACOLOGY RESEARCH UNIT (PPRU) NETWORK

Dr. Harry Shirkey first called attention to a major public health problem in children in 1968, when he noted that drugs used to treat diseases in children were not being tested in children for safety and efficacy. He coined the term "therapeutic orphans" to describe this population. Because drug companies have little economic incentive to study drugs in children, only one in five drugs prescribed for use in children has ever been tested in that population. When untested drugs are prescribed for children, this "off-label" usage not only puts the child at risk for adverse drug reactions, but it also puts the physician at risk for a medical malpractice suit. In 1995, the Committee on Drugs of the American Academy of Pediatrics noted that every time a physician prescribed an unlabelled drug for a child, he or she was performing an uncontrolled experiment with an enrollment of one and no protocol or outside overview. The Committee emphasized that it was unethical *not* to study drugs in children.

To address this problem, in 1994, the NICHD created the PPRU Network, composed of seven academic institutions, to demonstrate that pediatric drug studies could be performed in children ethically and efficiently. In the ensuing five years, the Network performed more than 100 studies in newborns, children, and adolescents.

To encourage pharmaceutical companies to study drugs in children, in 1997, Congress passed the FDA Modernization Act (FDAMA), which provided for a six-month extension of exclusivity for marketed drugs with remaining patent or any other kind of exclusivity if the pharmaceutical company conducted pediatric testing. In 2002, Congress replaced the FDAMA with the Best Pharmaceuticals for Children Act (BPCA), legislation that reauthorized extension of exclusivity for marketed drugs and also mandated studies of off-patent drugs in children. Another important provision of BPCA was the inclusion of newborns in pediatric drug studies. The Joint Conference Committee of the House and Senate recognized the PPRU Network as a national resource in the process of drafting the BPCA. To complement the BPCA in 2003, Congress passed the Pediatric Equity Research Act, which requires companies to test new molecular entities in children that may benefit pediatric populations.

The impact of FDAMA on Network-sponsored pediatric drug trials is reflected in the increase in the number of studies conducted within the PPRUs before and after the Act was passed. In 1998, the Network had 21 active protocols; by 2003, the number had risen to 92 protocols. From 1994 through June 2004, the total number of children in PPRU studies reached 5,960 in 216 protocols.

The PPRU Network has now performed labeling studies for 54 pharmaceutical sponsors both in the United States and abroad. Table 1 lists the pharmaceutical companies and the number of studies each company supported in the PPRU Network during this time frame. These studies have led to labeling for new pediatric indications for 75 drugs.

To accommodate the increased industrial demand for pediatric drug studies, the NICHD expanded the PPRU Network in January 1999, from seven to 13 units (see Figure 2). The Network has access to approximately 160,000 pediatric inpatient admissions and 2,300,000 outpatient visits annually. Figure 2 displays the current composition of the Network and the location of the Units.

In addition, the BPCA language specifically mentions the PPRU Network as a venue for performing off-patent drug studies. PPRU Network investigators have played prominent roles as expert consultants in the listing process required by the BPCA. For instance, PPRU researchers successfully competed for support to perform studies of the use of the off-patent drug lorazepam in children.

PPRU NETWORK RESEARCH IN DEVELOPMENTAL PHARMACOLOGY

The RFAs for the recompetition of the Units in the PPRU Network in 1998, and 2003, included new research requirements, including:

- Studies on drug metabolizing enzymes;
- Molecular approaches to the treatment of diseases;
- Application of new technology to drug-delivery systems; and
- Development of new pediatric formulations.

The most challenging aspect of performing drug trials in children is conducting efficacy studies in preterm and sick newborn infants. Studies have demonstrated the efficacy of only a few of the 140 drugs currently used in neonatal intensive care units. This population is the most vulnerable to adverse drug effects because of the immaturity of their drug-metabolizing enzymes and the pathophysiologic changes that affect drug disposition in these fragile patients.

Changes in the central pharmacologic paradigm from providing symptomatic relief to targeting the cause or mediators of disease makes understanding of developmental pharmacology mandatory. To address this issue, the ENGB sponsored a workshop on the subject and benefited from the participation of world experts in identifying research priorities. The Branch used the recommendations generated at the workshop to develop an RFA on developmental pharmacology.

Participants noted that the incidence of adverse drug reactions in pediatric populations was particularly understudied, even though such reactions are among the most common causes of death in hospitalized patients. New biomedical technology now permits the study of mechanisms that predispose patients to these reactions. For example, pharmacogenomic screening of patients may lead to the identification of genetic variations that lead to toxic

reactions. Researchers are now developing proteomic techniques to identify the specific proteins that serve as molecular markers of toxicity.

In 2002, the ENGB published an RFA soliciting projects on the molecular mechanisms involved in the production of adverse drug reactions in children. Projects funded in response to the RFA include studies of drug-induced pancreatitis, and studies of the bioactivation of some drugs into toxic metabolites.

TRAINING OPPORTUNITIES RESULTING FROM THE PPRU NETWORK

Each PPRU offers a teaching environment in which pediatricians, pharmacists, and others gain supervised experience and training in the methodology of pediatric clinical trials. Most PPRUs have arrangements with schools of pharmacy to offer training for both undergraduate and graduate pharmacy students in pediatric clinical pharmacology and drug trial methodology.

Implementation of pediatric drug trials also requires adequately trained study coordinators and research nurses. Currently, nurses learn special skills by trial and error because this type of training is not available in nursing degree programs. The PPRU Network is working with professional nursing organizations to plan formal training that teaches nurses the necessary skills for these studies.

There is also a dearth of pediatric clinical pharmacologists, and training opportunities for these professionals are scarce. To remedy this situation, the ENGB developed the Mentored Specialized Clinical Investigator Development Award in 1999. The objective of this fellowship is to provide skills in the design, execution, and interpretation of pediatric drug clinical trials, with emphasis in pharmacokinetic modeling, pharmacokinetic-pharmacodynamic correlations, and drug metabolism. So far, the Branch has funded six clinical pharmacologists with these awards. Their work focuses on studies related to the ontogeny of drug-metabolizing enzymes and the pharmacodynamics of antimicrobial agents.

THE NEWBORN DRUG DEVELOPMENT INITIATIVE

As part of the effort to implement provisions of the BPCA, the ENGB is collaborating with the FDA on the Newborn Drug Development Initiative. This initiative is exploring innovative approaches to improve clinical trial design for preterm and full-term neonatal populations, with the goal of having more drug therapies studied and appropriately labeled for safe and effective use in these vulnerable populations.

The first phase of the initiative began with the formation of work groups in February 2003, and culminated in the first workshop held in Baltimore in March 2004. This first phase addressed ethics and drug prioritization, as well as the therapeutic areas of pain control and pulmonary, cardiovascular, and neurological diseases or conditions. The next phases will include studies of drugs used to treat infectious and gastrointestinal disorders in the pediatric population, as well as studies of developmental toxicology.

OBSTETRIC-FETAL PHARMACOLOGY RESEARCH UNIT (OPRU) NETWORK

The study of drugs used during pregnancy is one of the most neglected areas in the fields of clinical pharmacology and drug research. Implementation of legislation has enabled researchers to make great strides in solving the problem of children as therapeutic orphans; pregnant women now constitute the only remaining group to which the label of therapeutic orphans can be meaningfully applied. To address this problem, the NICHD issued an RFA in July 2003, to initiate the OPRU Network, an effort modeled after the PPRU Network that will explore the safety and efficacy of obstetric drug therapies.

CREATION OF THE OBSTETRIC AND PEDIATRIC PHARMACOLOGY BRANCH (OPPB)

To focus on the burgeoning research agendas in the fields of obstetric, fetal, neonatal, and pediatric pharmacology, and to address the legislative mandates embodied in the BPCA, the NICHD established the OPPB in June 2004. The new Branch now encompasses the PPRU Network and the newly created OPRU Network, as well as all BPCA-related activities and the research programs devoted to developmental pharmacology and adverse drug reactions.

THE CHILD HEALTH RESEARCH CAREER DEVELOPMENT AWARD (CHRCDA) PROGRAM

The CHRCDA Program, now beginning its fifteenth year, emerged through congressional action stimulated by efforts of the National Association of Children's Hospitals and the Pediatric Research Societies. The goal of the Program is to establish Centers of Excellence in pediatric research. When the Program began in 1990, the NICHD funded six pediatric departments and children's hospitals. By 1992, the number increased to 19 centers, and an additional center was added in 1997. The current 20 centers in the Program (see Figure 5) are funded by K12 awards, which provide five-year funding for new research projects conducted by nascent pediatric investigators, as well as core support for laboratory and administrative resources.

The CHRCDA Program divides its resources between the support of well-funded existing pediatric departments and the development and stimulation of new centers that demonstrate potential. Program funds provide an ideal environment for learning, while nurturing young scientists into the forefront of pediatric research. In each center, established investigators make available their expertise and laboratory facilities to junior investigators to help hone research skills. This experience also enables junior researchers to generate preliminary data that they can include in grant applications for independent funding. The Program functions as the Institute's investment in the future of pediatric research and physician-scientist development.

Since its inception, the Program has supported 28 pediatric departments and 485 pediatric investigators in 14 different subspecialty areas. The areas of greatest concentration include hematology/oncology, neonatology, genetics, and infectious diseases. This elite group includes two department heads, 20 tenured professors, and 75 tenure-track associate professors; in addition, 36 percent of these investigators are women, and 16 percent belong to minority groups. Only 11 percent of this group reports spending less than 10 percent of their time in research.

One measure of the Program's success is attaining competitive NIH research grants. Some 40 percent of Program scholars have succeeded in obtaining NIH grant support. The most successful centers, as measured by their ability to produce investigators who obtain independent NIH funding, include Yale University, the University of Michigan, Children's Hospital of Philadelphia, and the Children's Hospital Medical Center in Cincinnati. Subspecialty areas that yielded the highest NIH funding success rates include infectious diseases, endocrinology, and hematology/oncology (Winer et al 2002).

NATIONAL RESEARCH SERVICE AWARD TRAINING PROGRAM

Since the Institute's founding, a principal objective of the NICHD has been to support the training of junior investigators and to promote interdisciplinary training opportunities through individual postdoctoral fellowships, institutional training grants, and career awards. The Institute awards individual postdoctoral fellowships (F32s) to newly trained scientists for up to three years, enabling them to work full-time with a qualified mentor to develop expertise in research. The NICHD also awards institutional training grants (T32s) to outstanding institutions that show potential to establish or maintain an exceptional environment for research training. The purpose of the National Research Service Awards Training Program is to enhance postdoctoral research training in both basic and clinical research. The Institute initiated a new T32 program in September 2001, in response to the Children's Health Act of 2000, which encouraged the initiation of subspecialty programs to train pediatricians. The Program began in 2002, supporting six centers, and more than doubled in size in 2003, to support 13 centers (see Figure 4).

CONCLUSION

The past four years have witnessed remarkable discoveries in the areas of single-gene defects, transposable elements, genomics, and high-throughput screening techniques for CAH and T1DM. These advances will be exploited with the aim of developing gene rescue therapy for single-gene defects, such as CAH and some disorders of sex reversal. Advances in understanding how bone MSCs can be stimulated to differentiate into functioning neurons will be expanded with the ultimate aim of reversing neurological diseases. The discovery of the

antimicrobial activity of oligosaccharides in human breast milk will also be exploited to develop a new class of antibiotics.

The research encouraged and supported by the ENGB has contributed to the health of children in the United States and abroad by establishing standards of growth and of nutrient requirements during development. The ENGB plans to continue this work by establishing standards of skeletal accretion during childhood and adolescence, and by defining nutrient requirements for IUGR infants and for babies born preterm.

The Branch also supported pioneering research that establishes criteria for the use of hGH in various kinds of growth retardation; it will continue to elucidate the genetic-environmental interactions involved in the pathogenesis of retarded growth, and in the phenomenon of catch-up growth. The Branch will also focus on establishing the most effective and appropriate hormonal treatments for a wide variety of growth-retarding conditions.

The ENGB also pioneered methods in ascertaining genotype-phenotype correlations in disorders caused by single-gene mutations. The Branch will expand this work to encompass polygenic disorders, such as obesity and diabetes. The Branch has also developed immunogenetic biomarkers for T1DM that are now in use all over the world. This landmark work will form the basis of future diagnostic programs that utilize high-throughput genomic and proteomic techniques.

The Branch has also led the expansion of the field of the fetal origins of adult disease and will continue this research by focusing on the effects of excess adiposity during pregnancy on the metabolic and developmental health of the offspring of such pregnancies. The Branch will also encourage research on the intergenerational transmission of metabolic disease from mother to daughter, in both animals and humans.

The Branch currently supports several large, international research projects on T1DM, GDM, and the effects of micronutrient supplementation on health and development. ENGB staff will encourage the expansion of these international research endeavors in the coming years.

The ENGB remains committed to ascertaining the earliest origins of disease and to developing effective interventions to assure the healthiest possible future for children in the United States and abroad.

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FIGURES AND TABLES

FIGURE 1: BRANCH-SUPPORTED PROJECTS, FISCAL YEAR 2003

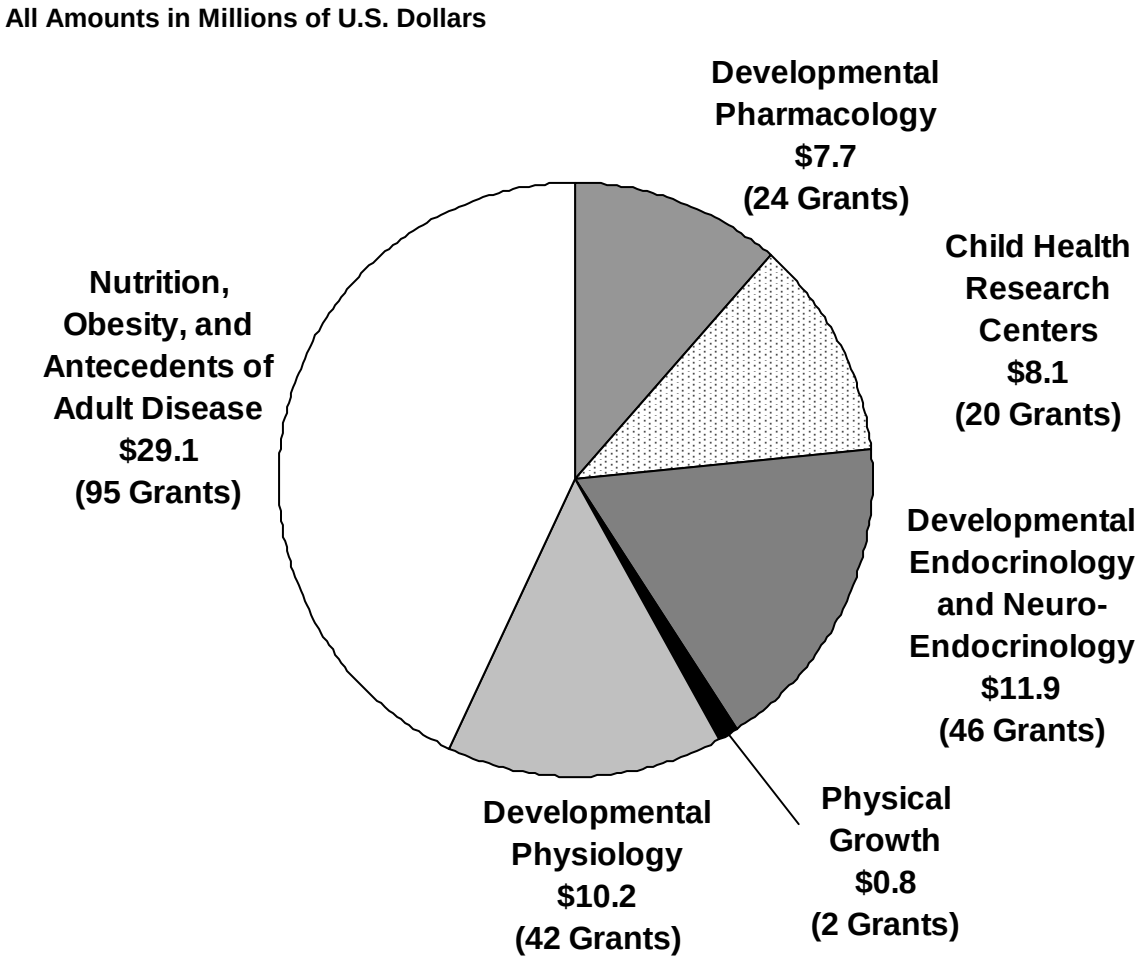


FIGURE 2: PEDIATRIC PHARMACOLOGY RESEARCH UNIT (PPRU) NETWORK

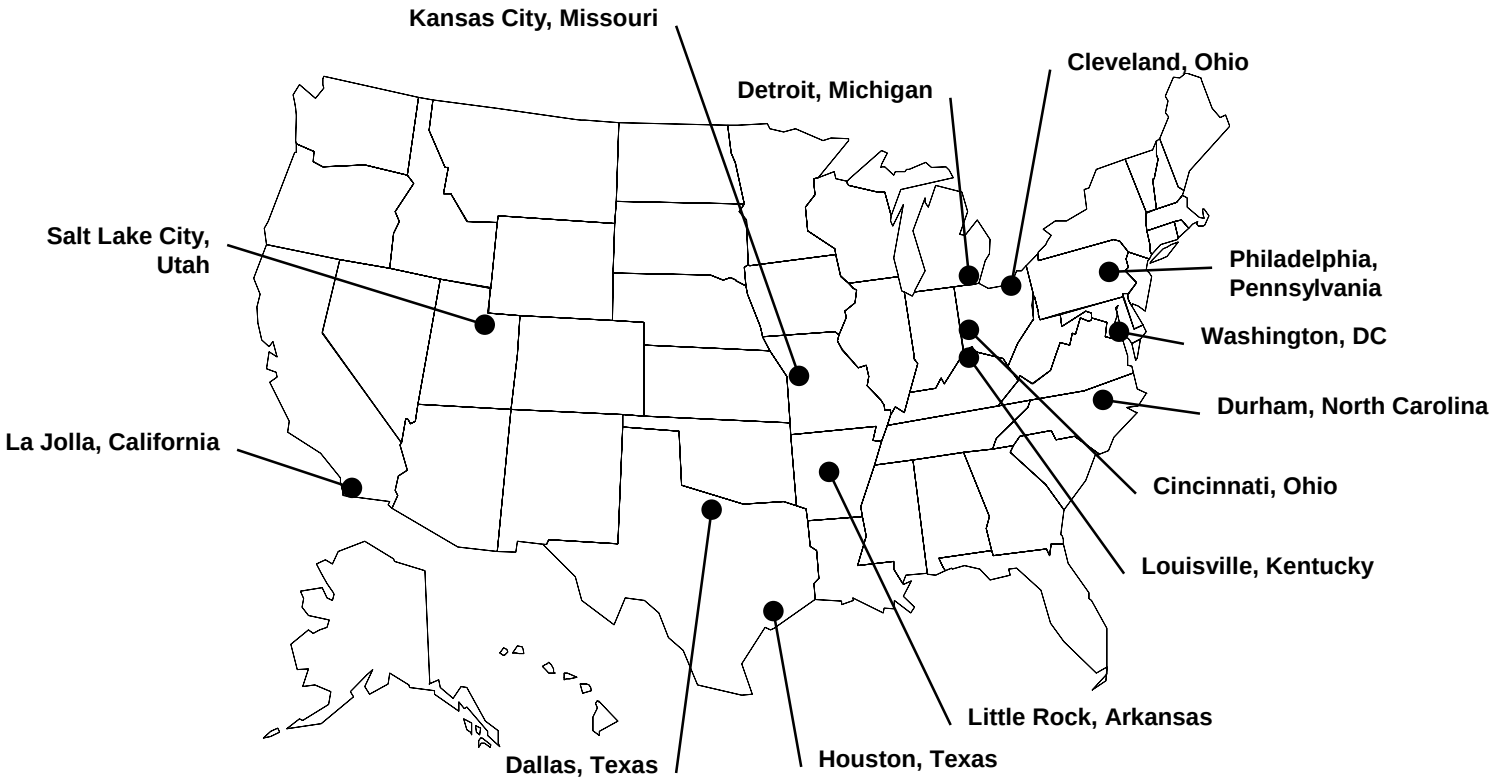
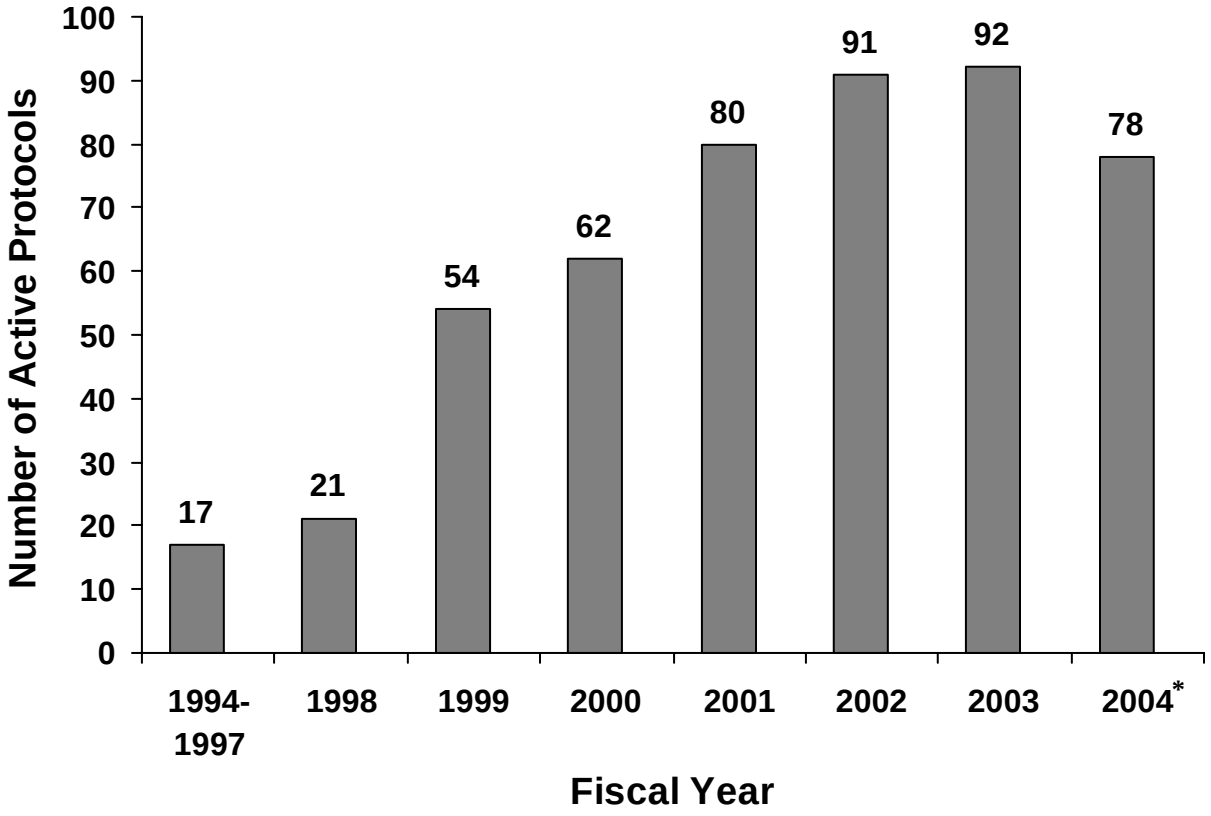


TABLE 1: PHARMACEUTICAL COMPANIES AND STUDIES DONE IN THE PPRU NETWORK

Pharmaceutical Company	Number of Studies
3M Pharmaceuticals	1
Abbott Laboratories	3
Alcon Research, Ltd.	1
Amgen, Inc.	4
Aronex Pharmaceuticals	1
AstraZeneca LP	7
Aventis Behring L.L.C.	1
Aventis Pharmaceuticals	8
Baxter Pharmaceutical	2
Becton Dickinson, Inc.	1
Boehringer Ingelheim	1
Bristol-Myers Squibb Co.	13
Byk Gulden Pharmaceuticals	1
Centocor Inc	2
Eisai Medical Research Inc	1
Eli Lilly	1

Pharmaceutical Company	Number of Studies
Farmacon	1
Ferndale Laboratories, Inc.	1
Fujisawa Health Care, Inc.	2
Gate Pharmaceuticals	1
Gilead	1
GlaxoSmithKline	12
Hoffmann-LaRoche, Inc.	2
ICN Pharmaceuticals	1
ILEX Oncology, Inc.	2
Janssen Pharmaceutical	5
Johnson & Johnson	1
King Pharmaceuticals, Inc.	2
Laboratories UPSA	1
Luitpold Pharmaceuticals, Inc.	1
Mallinckrodt	1
MedImmune, Inc.	3
Merck & Co., Inc.	17
MiniMed	2
Novartis Pharmaceuticals Corporation	7
Novo Nordisk Pharmaceuticals, Inc.	1
Parke Davis	2
Pfizer, Inc.	6
Pharmacia & Upjohn, Inc.	9
Purdue Pharma, L.P.	3
R.W. Johnson Pharmaceutical Research Institute	11
Reliant Pharmaceuticals	1
Sage Pharmaceutical	1
Sanofi-Synthelabo	2
Schering-Plough Research Institute	1
Sepracor, Inc	2
Takeda Pharmaceuticals America, Inc.	1
TAP Pharmaceuticals	1
Triangle Pharmaceuticals Inc.	1
UCB Pharma Inc	1
Unimed Pharmaceuticals	1
ViroPharma	3
Whitehall Robbins Healthcare	2
Wyeth Ayerst	6
Zars, Inc.	1

FIGURE 3: NUMBER OF ACTIVE PROTOCOLS IN THE PPRU NETWORK, FISCAL YEARS 1994 THROUGH 2004



* Note: 2004 data span 01/01/2004 through 10/31/2004.

FIGURE 4: NATIONAL RESEARCH SERVICE AWARD INSTITUTIONS (T32S)

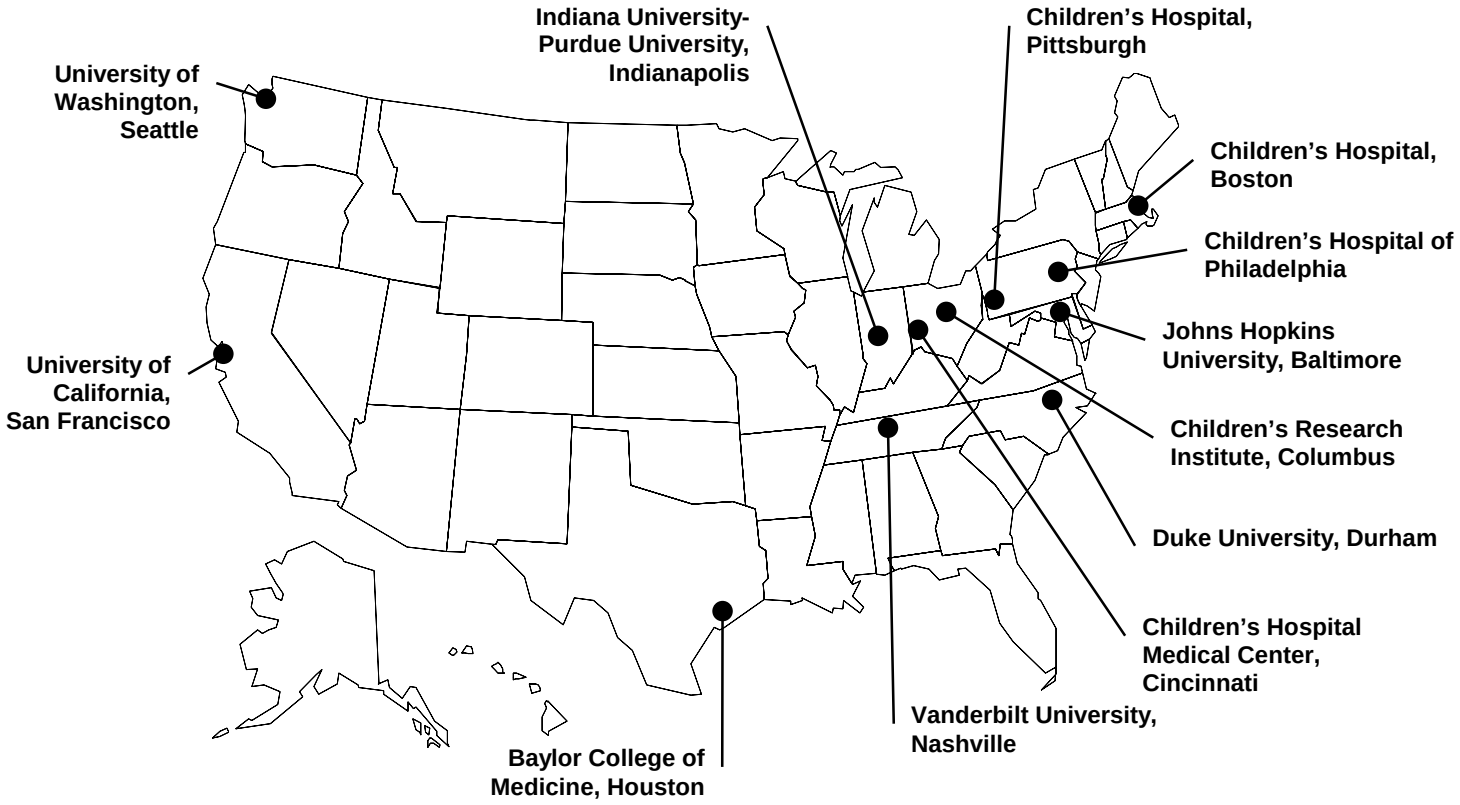
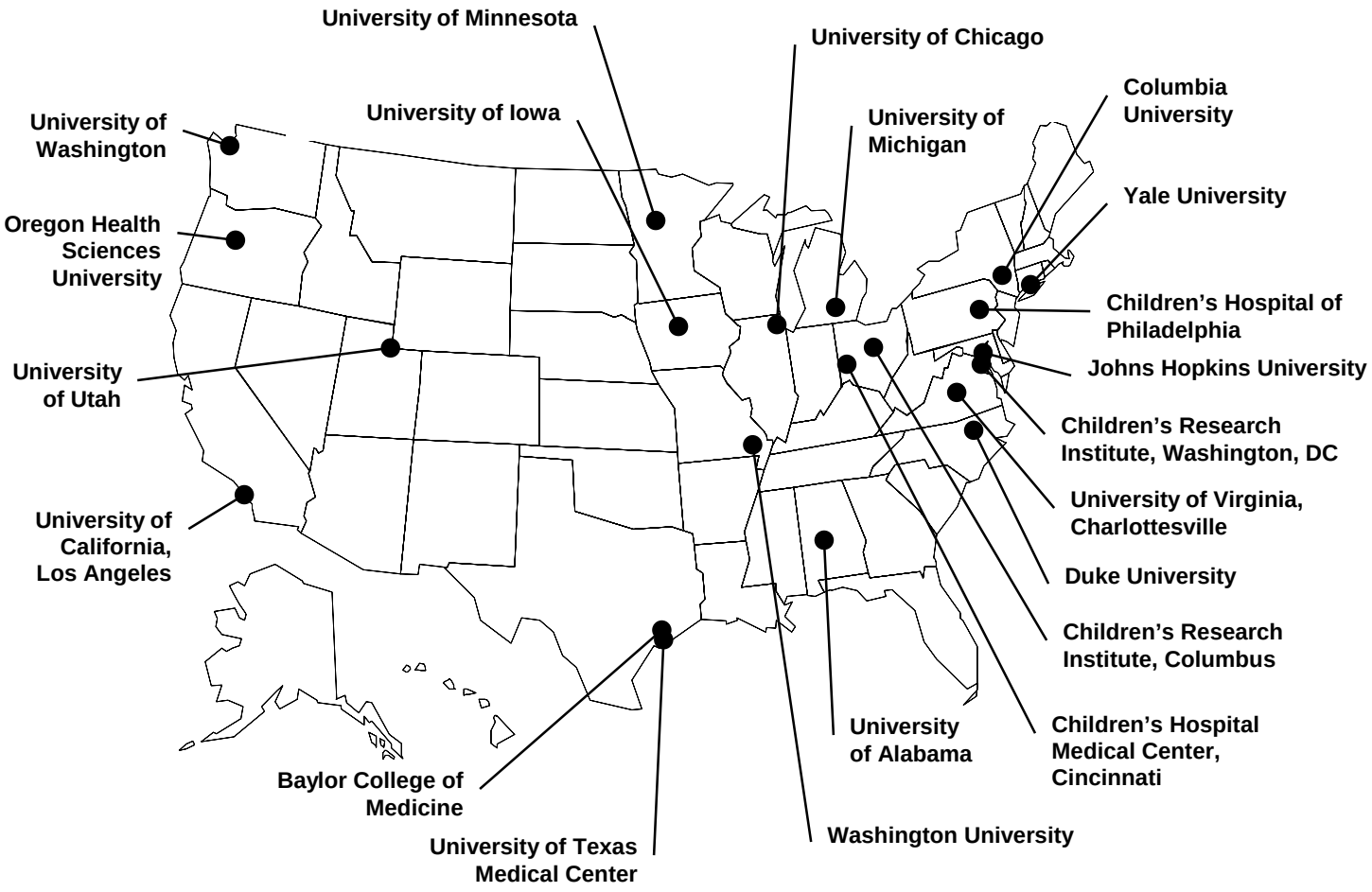


FIGURE 5: CHILD HEALTH RESEARCH CENTERS (CHRCS), FISCAL YEAR 2003



APPENDIX A: BRANCH-SUPPORTED CONFERENCES AND WORKSHOPS

(Includes Sponsored and Co-Sponsored Events)

- *Annual Child Health Research Centers (CHRC) Meeting*, University of Utah, September 12-14, 2005
- *Pharmacological Agents and Their Effects on the Pediatric Skeleton*, April 14, 2005
- *Current Topics in Neonatal and Infant Nutrition: Methionine Metabolism and Epigenetics*, January 11-12, 2005
- *Islet Cell Transplant: Prelude to the Future*, December 1-2, 2004
- *NIH State-of-the-Science Conference on the Role of Multivitamin/Multimineral Supplements in Chronic Disease Prevention Planning Meeting*, October 19-20, 2004
- *Annual CHRC Meeting*, University of Michigan, October 15-17, 2004
- *Rare Diseases in Pediatrics: Definition and Relationship to Orphan Drugs*, September 27-28, 2004
- *Site-Specific Approaches: Prevention on Management of Pediatric Obesity*, July 14-15, 2004
- *NIH Consensus Development Conference on Celiac Disease*, June 28-30, 2004
- *Modifiable Environmental and Behavioral Determinants of Overweight Among Children and Adolescents*, June 22-23, 2004
- *Robert Wood Johnson Foundation Conference: Health Care Strategies for Addressing Childhood Obesity*, June 10, 2004
- *Extrapolation of Non-Clinical Data to Pediatric Clinical Studies*, June 4-6, 2004
- *Advances in Skeletal Anabolic Agents for the Treatment of Osteoporosis*, May 24-25, 2004
- *Lipids and the Pathophysiology of Obesity*, May 10-11, 2004
- *Neonatology Initiative Workshop*, March 29-30, 2004
- *Vitamin D and Health in the 21st Century: Bone and Beyond*, October 11-12, 2003
- *Maternal and Child Health in the America, Fifth Annual Lawton Chiles Lecture*, October 3, 2003
- *Annual CHRC Meeting*, Oregon Health Science Center, September 12-14, 2003

- *Establishing the Precursors of the Metabolic Syndrome in Childhood*, June 30-July 1, 2003
- *The Menstrual Cycle and Bone Health Meeting*, May 22, 2003
- *Newborn Initiatives for Neonatal Drug Development*, February 10, 2003
- *Current Topics in Neonatal and Infant Nutrition: Evidence-Based Nutrient Supplementation*, January 14-15, 2003
- *Annual CHRC Meeting*, Washington University, October 25-27, 2002
- *Research-Planning Workshop on Intersex*, May 19-20, 2002
- *Hormonal and Genetic Basic of Sexual Differentiation Disorder*, May 18-21, 2002
- *Drugs in Breast Milk*, April 24-26, 2002
- *Dietary Supplement Use in Women: Current Status and Future Directions*, January 28-29, 2002
- *Fat Metabolism in Fetal and Neonatal Nutrition*, January 8-9, 2002
- *Annual CHRC Meeting*, Columbia University, November 9-11, 2001
- *Dietary Supplement use in Children: Who, What, Why and Where Do We Go from Here*? February 12-13, 2001
- *Glucose/Carbohydrate Metabolism in the Newborn Infant*, December 12-13, 2000
- *Clinical Pharmacology During Pregnancy: Addressing Clinical Needs Through Science*, December 4-5, 2000
- *Annual CHRC Meeting*, Johns Hopkins University, November 2000
- *Risk Factors in Childhood for Atherosclerosis Later in Life*, September 27-29, 2000
- *The Use of Drugs in Pregnancy*, September 23-24, 2000
- *Nutrition and Health of Women, Infants and Children in India*, February 10-12, 2000
- *Bioavailability of Nutrients and Other Bioactive Components of Dietary Supplements*, January 5-6, 2000
- *Protein/Nitrogen Metabolism and Accretion in Very Low Birth Weight Infants*, November 18-19, 1999
- *Developmental Pharmacology*, October 25-26, 1999

APPENDIX B: DIRECNET PUBLICATIONS

DirecNet Study Group. (2003). The accuracy of the Continuous Glucose Monitoring System (CGMS®) in children with type 1 diabetes: results of the Diabetes Research in Children Network (DirecNet) Accuracy Study. *Diabetes Technology and Therapeutics, 5*(5): 781-789.

DirecNet Study Group. (2003). The accuracy of the GlucoWatch® G2TM biographer in children with type 1 diabetes: results of the Diabetes Research in Children Network (DirecNet) Accuracy Study. *Diabetes Technology and Therapeutics, 5*(5): 791-800.

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DirecNet Study Group. (2004). GlucoWatch® G2™ Biographer (GW2B) alarm reliability during hypoglycemia in children. *Diabetes Technology and Therapeutics, Aug;6*(4): 559-566.

DirecNet Study Group. (In press). Comparison of finger-stick hemoglobin A_{1c} levels assayed by DCA 2000 with the DCCT/EDIC central laboratory assay: results of a Diabetes Research in Children Network (DirecNet) Study. *Pediatric Diabetes*.

DirecNet Study Group. (In press). Accuracy of the modified Continuous Glucose Monitoring System (CGMS®) sensor in an outpatient setting: results from a Diabetes Research in Children Network (DirecNet) Study. *Diabetes Technology and Therapeutics*.

DirecNet Study Group. (In press). A randomized multicenter trial comparing a real-time continuous glucose monitor with standard glucose monitoring in children with type 1 diabetes. *Journal of the American Medical Association.*

DirecNet Study Group. (In press). Diabetes self-management profiles for flexible regimens: cross-sectional and longitudinal analysis of psychometric properties in a pediatric sample.

DirecNet Study Group. (In press). Youth and parent satisfaction with clinical use of the GlucoWatch® G2™ Biographer (GW2B) in the management of pediatric type 1 diabetes.

ABSTRACTS, POSTERS, AND PRESENTATIONS

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APPENDIX C: BONE MINERAL DENSITY IN CHILDHOOD STUDY (BMDCS) PRESENTATIONS

Horlick M, Lappe JM, Gilsanz V, Kalkwarf HJ, Zemel BS, Mahboubi S, Shepherd JA, Frederick MM, Winer K. (2004 October). The Bone Mineral Density in Childhood Study (BMDCS): Baseline Results for 1554 Healthy Pediatric Volunteers. Presented at the 26th Annual Meeting of the American Society of Bone and Mineral Research in Seattle, WA.

Shepherd J, Fan B, Sherman M, Winer K. (2004 June). Precision for Pediatric DXA Scan Modes. Presented at the 16th International Bone Densitometry Workshop in Annecy, France.

Shepherd J. (2004 October). Invited plenary lecture: bone densitometry in children. Presented at the International Osteoporosis Conference in Beijing, China.

Shepherd JA, Fan B, Sherman M, Gilsanz V, Horlick M, Kalkwarf H, Lappe J, Mahboubi S, Zemel B, Frederick M, Winer K. (2004 October). Pediatric DXA precision varies with age. Presented at the 26th Annual Meeting of the American Society of Bone and Mineral Research in Seattle, WA.

Wren TAL, Gilsanz V, Pitukcheewanont P, Liu X, Horlick M, Lappe JM, Kalkwarf H, Zemel BS, Mahboubi S, Shepherd JA, Frederick MM, Winer K. (2004 October). The Bone Mineral Density in Childhood Study (BMDCS): substudy comparing DXA and CT vertebral bone measurements in healthy children and adolescents. Presented at the 26th Annual Meeting of the American Society of Bone and Mineral Research in Seattle, WA.

APPENDIX D: HISTORY OF RESEARCH ON EPIDERMAL GROWTH FACTOR (EGF): R01 HD 00070-35

EGF is a polypeptide of 53 amino-acid residues that was isolated, purified, and sequenced by Dr. Stanley Cohen of Vanderbilt University between 1963 and 1974. He attained a major conceptual milestone when he found that a tyrosine kinase co-purifies with the EGF receptor protein. This key observation led to the discovery that the intracellular domain of the EGF receptor is a tyrosine kinase. With this finding, the growth factor field took on much broader significance because the protein product of the Rous avian sarcoma virus was also known to be a protein kinase. Eventually, this work led to a union of the fields of oncogenes and growth factors; this union, in turn, and helped to explain how both sets of effectors work.

In 1984, the fields of oncogenes and growth factors were shown to be even more closely related, when a striking sequence homology was noted between the tyrosine-kinase domain of the EGF receptor protein and the transforming gene product of the avian erythroblastosis virus. In fact, the oncogene product resembles a truncated EGF receptor protein that lacks the extracellular EGF binding domain, which governs the activity of the intracellular tyrosine kinase. Without its governing extracellular receptor domain, the intracellular protein kinase operates constitutively and causes cellular neoplastic transformation. The EGF receptor is activated by several of the ligands involved in normal breast development and lactation and is aberrantly expressed in breast cancers, especially in those with poor prognoses. As a result of this observation, health care providers use the EGF family of receptors in planning treatment regimens for women with breast cancer.

Research conducted over a 35-year period of NICHD funding, from 1964 through 1999, led to many biomedical advances, including:

- The discovery of 20 other structurally related growth factors, such as heregulin and amphiregulin, that are involved in mammary gland neoplasia;
- The use of EGF to treat corneal ulcers by accelerating epithelial regeneration;
- The use of EGF to treat severe burns by augmenting epithelial growth;
- Prevention of the onset of NEC in a newborn rat model; these findings were promising enough to consider implementing a trial of EGF in preterm babies at risk for NEC; and
- The understanding of the mechanism of receptor action for insulin and platelet-derived growth factor; this productive research was recognized internationally in 1986, when the Nobel Prize for Physiology or Medicine was awarded to Stanley Cohen of Vanderbilt University.

Cohen S. (1997). EGF and its receptor: Historical perspective. *Journal of Mammary Gland Biology and Neoplasia, 2*: 93-96.

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APPENDIX F: BRANCH SOLICITATIONS

(Includes Sponsored and Co-Sponsored Solicitations)

REQUESTS FOR APPLICATIONS (RFAS)

- RFA HD-97-006: *Prevention of Osteoporosis*
- RFA HD-98-002: *Network of Pediatric Pharmacology Research Units*
- RFA HD-98-008: *Behavioral Strategies in Children and Adolescents to Prevent Osteoporosis Later in Life*
- RFA DK-98-010: *Immunopathogenesis of Type 1 Diabetes*
- RFA DK-99-010: *Innovative Approaches to Prevention of Obesity*
- RFA HD-99-010: *Child Health Research Career Development Awards*
- RFA DK-00-008: *Type 2 Diabetes in the Pediatric Population*
- RFA AI-00-016: *Cooperative Study Group for the Prevention of Autoimmune Disease*
- RFA HD-00-020: *Child Health Research Career Development Awards*
- RFA HD-00-021: *Fetal Origins of Adult Disease*
- RFA HD-01-009: *Cooperative Multicenter Research Network to Test Glucose Sensors in Children with Type 1 Diabetes*
- RFA HD-01-018: *NICHD Institutional Training for Pediatricians*
- RFA HD-01-019: *Child Health Research Career Development Awards*
- RFA HD-01-025: *Clinical Research Network on Non-alcoholic Steatohepatitis (NASH)*
- RFA HD-02-001: *Mechanisms of Adverse Drug Reactions in Children*
- RFA HD-02-019: *NICHD Institutional Training for Pediatric Care*
- RFA DK-02-029: *Consortium for Identification of Environmental Triggers of Type 1 Diabetes*
- RFA HD-03-001: *Pediatric Pharmacology Research Unit Network*
- RFA HD-03-017: *Obstetric-Fetal Pharmacology Research Units*
- RFA DK-03-024: *Proteomics and Metabolomics in Type 1 Diabetes and its Complications*

- RFA ES-04-003: *Obesity and the Built Environment*
- RFA DK-04-013: *Site-Specific Approaches to Prevention or Management of Pediatric Obesity*
- RFA HD-04-020: *Prevention and Treatment of Childhood Obesity in Primary Care Settings*

PROGRAM ANNOUNCEMENTS (PAS)

- PA HD-03-163: *Nutrition and Development, Treatment, and Prevention of HIV/AIDS Disease in Women, Infants, and Children* (In conjunction with the NICHD Pediatric, Adolescent, and Maternal AIDS Branch)
- PA HD-04-145: *School-Based Interventions to Prevent Obesity*

APPENDIX G: BRANCH STAFF

Gilman Grave, M.D., is a graduate of Harvard College and Harvard Medical School. He is board certified in internal medicine, having completed an internship and residency in this field at the Massachusetts General Hospital that included six months of pediatrics on the Burnham ward. As a research associate and staff fellow at the NIH, Dr. Grave worked in the Laboratory of Cerebral Metabolism on brain imaging with radio-labeled 2-deoxyglucose. Since 1985, Dr. Grave has served as chief of the ENGB, which supports basic and clinical research on developmental endocrinology, nutrition, and growth of infants and children, within the NICHD. Dr. Grave leads a large research program on the childhood origins of adult diseases, and he is especially interested in disease prevention and in ascertaining the earliest antecedents of obesity, type 1 and type 2 diabetes, atherosclerosis, and osteoporosis. He has encouraged multidisciplinary research in these areas and recently initiated a research program on the fetal origins of adult disease. Dr. Grave is a member of the Working Group on Blood Pressure in Children and Adolescents for the National High Blood Pressure Education Program, chairs the NICHD Institutional Review Board, and represents the Institute on the NIH Human Subjects Research Advisory Committee. He also serves on the Subcommittee on Research Involving Children for the Secretary's Advisory Committee on Human Research Protection. In this capacity he drafted the NIH response to questions regarding the adequacy of federal regulations to protect children involved in research projects in the Children's Health Act of 2000. Dr. Grave also served as task leader for the Institute of Medicine's report *Ethical Conduct of Clinical Research Involving Children*, which was mandated by the BPCA in 2002. For these accomplishments Dr. Grave has been awarded the USPHS Commendation, Outstanding Service, and Meritorious Service Medals.

Daniel J. Raiten, Ph.D., joined the NICHD Office of Prevention Research and International Programs (OPRIP) in November 1999, and joined the program staff of the ENGB in December 2003. Within the ENGB, Dr. Raiten is responsible for supporting the nutrition-related activities of the Branch, including: obesity, infant and child feeding, clinical nutrition/care and prevention of low birth weight, the role of micronutrient in health and child development, and the expansion of programs focusing on nutrition and HIV/AIDS particularly in resource-limited settings. He also serves as a scientific resource and liaison to the NICHD director and staff on a broad range of issues in prevention and international research, under the auspices of OPRIP. Additional responsibilities for both ENGB and OPRIP include the development of agenda-setting conferences designed to address emerging issues in prevention and international health research, such as conferences on: dietary supplement use in infants and women; the emerging areas of importance of vitamin D to health; and the role of nutrition for health of women, infants, and children in India. He received his doctorate in human nutrition from the Pennsylvania State University and did a postdoctoral fellowship at the Child Study Center of Yale University Medical School. Dr. Raiten has a broad background in basic and applied aspects of nutrition, including extensive analytical/laboratory and clinical experience with an emphasis on behavioral, neurophysiological, and neurochemical assessment methodologies. His professional experience has largely focused on the study of the interactions of environmental and nutritional factors that

might impact on the physical and behavioral development of infants, children, and adolescents. A recent co-recipient of the DHHS Secretary's Award for Distinguished Service, Dr. Raiten has been involved in the development of workshops convened to bring scientists from various disciplines together to evaluate current trends and needs in topics of medical importance, and has served on both domestic and international advisory committees that address a range of issues in infant and child health and nutrition.

Karen Winer, M.D., a board-certified pediatric endocrinologist, is a program officer for the Pediatric Endocrinology and Osteoporosis Prevention Programs in the ENGB. She completed her pediatric residency training at the Mount Sinai Medical Center, in New York, and went on to receive subspecialty training in pediatric endocrinology from the Developmental Endocrinology Branch of the NICHD. As an endocrine fellow, she was the first to demonstrate the safety and efficacy of synthetic human parathyroid Hormone (PTH) for the treatment of hypoparathyroidism. She remains at the forefront in investigating the long-term effects of PTH on bone. As a program officer, she is responsible for training grants and for the endocrine and bone programs. She is also the project officer for the BMDCS and for DirecNet.

Chrisoula Jennings serves as the program assistant for the Endocrinology, Nutrition and Growth Branch. Ms. Jennings joined the Department of Defense in 1990 and she received a Bachelor's degree in Child Psychology in 1998 from the University of Maryland Armed Forces European Division. She assisted Colonel Byrnes in the 5th Medical Group in the Air Force Base in Minot, North Dakota, Anderson Hospital "Best in the Air Force". She received the Cold War Certificate from the Secretary of Defense in appreciation of her distinguished service to the United States Air Force in the Gulf War 1990 through 1992. As the program assistant for the Branch she is responsible for maintaining grant files and records and for communicating with grantees in regard to their research support. She has been invaluable to the Branch in the preparation of this and other reports. She is a member of the NICHD Workplace Improvement and Diversity Advisory Committee and serves as an active member of the NIH Diversity Council.